Chronic Fatigue Syndrome

from prevalence and perpetuating factors to cognitive behaviour therapy

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Chronic fatigue syndrome: from prevalence and perpetuating factors to cognitive behaviour therapy

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Contents

General introduction

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General introduction

Chronic Fatigue Syndrome is defined as 'an unexplained persistent or relapsing chronic fatigue that is not the result of ongoing exertion, is not substantially alleviated by rest, and results in a substantial reduction in previous levels of occupational, educational, social, or personal activities'[1]. Since 1990 the Nijmegen Fatigue Research Group (NFRG), a collaboration of the Departments of General Internal Medicine, Medical Microbiology and Medical Psychology of the University Medical Centre Nijmegen St Radboud (UMCN), has been involved in research on the chronic fatigue syndrome. The studies presented in this thesis are all related to the development of the treatment manual 'Cognitive Behaviour Therapy (CBT) for Chronic Fatigue Syndrome (CFS)'. Included are studies on prevalence, perpetuating factors and the effect of CBT for CFS.

Chronic fatigue syndrome in general practice

Fatigue is a major problem in general practice. Studies show that 9% to 25% of the patients consulting their general practitioner (GP) complain of fatigue[2-9]. Most of this fatigue resolves within weeks. In CFS however the unexplained fatigue remains for at least 6 months. The prevalence of CFS in the Netherlands was unknown. Prevalence data are however important to assess disease burden and give directions for health policy. We investigated the prevalence of CFS in general practice, using questionnaire reports of GPs. Besides estimating the prevalence, our aim was to inform all GPs in the Netherlands about CFS. To prevent patients with Primary Fibromyalgia Syndrome (PFS) to be reported as CFS patients, the prevalence of PFS in general practice was studied at the same time. The results of this study are presented in ***chapter 2***.

Why do CFS patients remain so tired?

In early studies on CFS conducted by the NFRG, several hypotheses on microbiological and immunological causes were tested, but none proved to be an explanation for CFS[10-17]. Other hypotheses about physical and psychological causes of CFS had been formulated and studied, but no single cause of CFS could be detected[18]. Gradually, we became aware that research on pathogenesis might be more fruitful if facilitating, initiating and perpetuating factors for CFS were distinguished. Little is known about facilitating factors. The initiating factors are most likely heterogeneous: infection, anaesthesia, operation and psycho trauma are likely to play a role. However, most is known about the perpetuating factors. In a study by Vercoulen and colleagues a model of perpetuating factors in CFS was developed and tested[19]. It turned out that

a strong focus on bodily symptoms, low levels of physical activity and a low self-efficacy contributed to an increase in the severity of fatigue and functional impairment. Strong somatic attributions had only an indirect influence on fatigue, via lower levels of physical activity. These cognitive and behavioural perpetuating factors discovered by our group, were found in other studies as well[20-21].

Clinical observations suggested that at least some CFS patients also fulfilled criteria for Hyperventilation Syndrome (HVS). Because of a similarity in symptoms between CFS and HVS, it is conceivable that the physiological process held responsible for HVS, also plays an important role in CFS. For example, physiological hyperventilation may aggravate fatigue, which in turn may aggravate hyperventilation. If that is the case, this might have important consequences for CFS treatment. In ***chapter 3*** we addressed the question whether hyperventilation plays a role in CFS.

In 1989, Wessely and colleagues had formulated the hypothesis that CFS patients, experiencing a worsening of complaints after activity, learn to avoid activity in order to prevent an increase of complaints[22]. Consequently, inactivity might result in a decrease of physical fitness, and a worse physical fitness, in turn, might cause complaints to occur at increasingly lower levels of physical activity. In this way a perpetuating circle might be established. In ***chapter 4*** we investigated the question to what extent physical deconditioning occurs in CFS and how it relates to fatigue, impairment and physical activity.

Vercoulen and colleagues had found that cognitive factors, such as the expectancy that activity is harmful, were involved in producing low levels of activity in CFS[23]. Activities that patients expected to result in higher levels of fatigue were less frequently performed. Many CFS patients complain that after physical exercise their symptoms increase and that their level of activity decreases. Although CFS patients seem to have the belief that exercise is harmful, the actual effect of exercise on symptoms and activity in CFS was unclear. Therefore we studied the impact of exercise on symptoms and activity in CFS. Results of this study are presented in ***chapter 5***.

How to relieve fatigue in CFS? The effect of cognitive behaviour therapy

Several studies revealed that cognitions and behaviour are important perpetuating factors in CFS, suggesting a promising role for CBT in CFS. After some individual try-outs, the first publication of the NFRG on CBT for CFS, aiming at changing these perpetuating factors, appeared in 1994[24]. After successful preliminary individual treatments of CFS patients[25], controlled studies on the effect of CBT were set up. Our first study addressed the effect of cognitive behaviour group therapy (CBGT) for CFS. The main advantage of group therapy lies in the fact that several patients can be treated simultaneously. Modelling processes by seeing other members of the group might facilitate behaviour change. Aim of our controlled study on CBGT for CFS was to investigate the effect of CBGT for CFS on fatigue and impairment. Additionally pre-treatment characteristics of CFS patients who improve after CBGT were explored to investigate whether CBGT for CFS was only suitable for a subgroup of patients. This study, 'CBGT for CFS: a wait list controlled study', is presented in ***chapter 6***

Subsequently, the effect of individual CBT for CFS was studied in a large multi-centre randomised controlled trial. In earlier randomised controlled trials on the effect of individual CBT for CFS only a few highly skilled therapists or even a single therapist administered CBT in specialist centres. In our study CBT was administered in three different centres. Experts taught the treatment protocol to many therapists with no previous experience in CBT for CFS. CBT was compared with guided support groups and the natural course. Guided support groups should control for the absence of specific cognitive-behavioural interventions and the presence of therapist's attention and treatment expectations. Our hypothesis was that fatigue severity and functional impairment should decrease significantly more in the group of patients assigned CBT than in patients in the control groups. The study is presented in ***chapter 7***.
Besides examining the effect of CB(G)T for CFS, we wanted to know to what extent therapists adhered to the treatment manual and which perceptions they had of the treatment manual. Two questions were relevant. First, did the therapists, who were extensively trained and supervised, comply with the various aspects of the treatment manual during the actual sessions? Second, what is their judgment as to the treatments suitability for transfer? For this purpose, the therapists of the individual CBT study audio taped their sessions and filled in a questionnaire after completion of the study. Our aim was not only to have an integrity check, but also to use this information to further refine our treatment manual. In ***chapter 8*** the results of this study are presented.

Based on our knowledge gained from aforementioned studies, the treatment manual was adjusted. Treatment manuals used at the different stages of our studies have appeared in several publications[26-31]. The last version is presented in ***chapter 9***.
Finally, ***chapter 10*** covers a general discussion of the studies in this thesis. The role of activity in CFS is re-examined, ingredients of CBT for CFS are discussed, and the suitability of the treatment manual in various circumstances and settings is reviewed. Future directions are given.

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Chronic fatigue syndrome and primary fibromyalgia syndrome as recognized by GPs

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Abstract

Background. Prevalence studies on Chronic Fatigue Syndrome (CFS) are rare. Because of the similarity in symptoms, the prevalence of Primary Fibromyalgia Syndrome (PFS) was investigated at the same time.
Objectives. To determine the prevalence of CFS and PFS as recognized by GPs in The Netherlands and to inform them of the existence of CFS.
Methods. A postal questionnaire was sent to all GPs.
Results. The questionnaire was returned by 60% of the GPs. Seventy-three per cent reported one or more CFS patients and 83% one or more PFS patients in their practice.
Conclusion. The estimated prevalence of CFS as recognized by GPs of 112 (PFS 157) patients per 100 000 is a minimum estimate.

Introduction

Chronic Fatigue Syndrome (CFS) is described as severe fatigue which has persisted for more than six months, is not relieved by bed rest and leads to severe disability in daily life. A physical explanation for this condition has not yet been found. Various other complaints can accompany the fatigue, such as muscular pain, headache, memory and concentration problems, and depression. Despite extensive research, the cause of CFS is still unknown and the diagnosis is established by means of exclusion. For this reason, some physicians do not accept CFS as a disease. However, CFS has since been recognized as a disease by the World Health Organisation and has been included in the International Classification of Diseases (ICD 10).

Many of the symptoms of CFS are also characteristic of the Primary Fibromyalgia Syndrome (PFS). To prevent confusion, one has to inquire for both syndromes. In this article, the results of a study carried out among Dutch GPs are described. There were two major aims. The first was to gain insight into the number of CFS and PFS cases as recognized by GPs in the Netherlands. The second aim was to confront all GPs in The Netherlands with the existence of CFS and to give them information about this disease.

Method

All 6657 GPs in The Netherlands received a mailed questionnaire. A Dutch institute for health research (NIVEL) provided their names and addresses. In the questionnaire the GPs were asked to report the size of their practice, the number of CFS and PFS patients in their practice and the distribution of these patients according to age and sex. A text with a definition of CFS and PFS was included in the questionnaire. For CFS a complaint duration of one year was used. If a response was not received within six weeks, a reminder was sent.

Results

Response

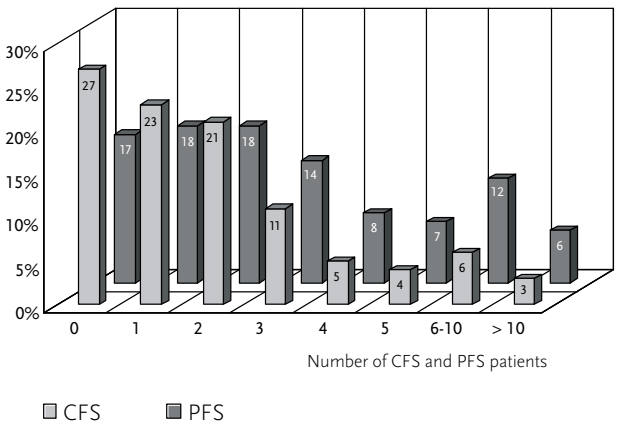
In total, 4027 questionnaires were returned (60.5%). Of the 4027 questionnaires 3881 (58.3%) were suitable for analysis. A reason for not completing or not filling in the questionnaire was given by 397 of these 3881 GPs. Twenty-seven of the responders (0.7%) said they "never make this diagnosis, find the diagnosis too difficult, or find the diagnosis insufficient", and 37 GPs (1.0%) said they "refuse to make this diagnosis or do not believe in this disease". Other reasons given for not completing the questionnaire were "I do not have my own patient database", "this is not a scientific study", "I do not participate in surveys", "I do not yet have insight", or "I will not review my patient data for this purpose".

Number of CFS and PFS patients as recognized by GPs

The frequency distribution of CFS and PFS patients in their practice, as reported by GPs, is shown in figure 1. Seventy-three per cent of the GPs stated that they had one or more CFS patients in their practice. Eighty-three per cent of the GPs reported that they had one or more PFS patients in their practice.

Figure 1

FREQUENCY DISTRIBUTION OF THE NUMBER OF CFS AND PFS PATIENTS IN THE GP'S PRACTICE



Since the size of the average practice, as indicated by the GPs, was 2486 patients, the number of CFS patients as recognized by GPs in The Netherlands is 112 per 100 000 inhabitants; for PFS, it is 157 per 100 000 inhabitants. Overall, 81% of the CFS patients and 87% of the PFS patients were female. Among CFS patients, 55% were between 25 and 44 years old versus 48% of the PFS patients.

Discussion

In this survey, GPs reported to recognize 112 CFS patients and 157 PFS patients per 100 000 inhabitants. This means that there are at least 17 000 CFS patients and 24 000 PFS patients in the Netherlands, in a total population of about 15 million inhabitants. The data obtained from this study were validated by comparing the age and sex of the CFS patients of this survey with those of a population of 298 CFS patients who were previously studied in detail by our research group[1]. In that cohort, 75% were female and 62% were between 25 and 44 years of age. The respective values for this study are 81 % and 55 %.

The prevalence rate based on recognitions by GPs in our study is considerably lower than those found in population-based studies, in which prevalence rates of up to 0.56 and 2.6%, respectively, were found[2-3]. Such differences may be due to a number of causes. Although a response rate of 60% can be considered high, the question is whether it can be considered representative for all GPs and whether the data can be generalized. It is likely that there were more GPs that did not accept this condition among the 40% non-responders than among the 60% responders. However, if a GP never establishes the diagnosis CFS, this does not mean that there are no patients with CFS in his practice. In addition, the GPs who did fill in the questionnaire may have been conservative in making the diagnosis. The fact that CFS was relatively unknown among GPs also played a role. It is quite likely that only those patients with an obvious diagnosis were included in this survey. If such a survey were to be repeated in the future, then one might expect that a higher number of CFS patients will be recognized by GPs because the presentation of information leads to better recognition. Furthermore, in the present study a fairly conservative definition of CFS was used as far as the duration of the complaints: a fatigue persisting for at least one year. This was applied because we had the impression that a number of patients recover within six months to a year. If the label CFS is attached to these complaints at an early stage, this may have the effect of perpetuating the complaints. However, in the current agreement on the CDC criteria, in which our group also participated, duration of the complaints is six months. This is another reason why the number of CFS patients found in our study will be a low estimate of the number of CFS patients in the Netherlands.

If we take into consideration the fact that 1% of the GPs refuse to establish this diagnosis or do not believe in the disease and that 0.7% do not make the diagnosis or find the condition too difficult to diagnose, then acceptance of the diagnosis CFS is not as poor as is so often suggested. This was also concluded by Denz and Murdoch, who found that the clinical validity of chronic fatigue syndrome was accepted by 90% of the GPs in Otago, New Zealand[4]. Fitzgibbon and

colleagues found that CFS as a distinct clinical entity was accepted by 58% of the GPs in Ireland, and that 82% would consider a diagnosis of CFS in their own patients with chronic debilitating fatigue[5]. In view of the 60% response rate and the generally positive reactions in our study, it can be said that the aim of confronting and informing all Dutch GPs about the existence of CFS was achieved. Nevertheless, there are still more GPs that diagnose PFS (83%) than diagnose CFS (73%). It is of interest that 27% of the GPs who do not diagnose CFS 65 % still diagnose PFS. Of the 17% of the GPs that do report not to have PFS patients in their practice, only 46% diagnose CFS. Because CFS and PFS are rather similar diagnoses, this may indicate that PFS is more accepted than CFS.

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The chronic fatigue syndrome and hyperventilation

3

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Abstract

Chronic fatigue syndrome (CFS) is characterized by severe fatigue, lasting for at least six months, for which no somatic explanation can be found. Because hyperventilation can produce substantial fatigue, it seems worthwhile to investigate the relationship between it and CFS. It might be hypothesized that hyperventilation plays a causal or perpetuating role in CFS. CFS patients, non-CFS patients known to experience hyperventilation, and healthy controls were compared on complaints of fatigue and hyperventilation. CFS patients and non-CFS patients known to experience hyperventilation offered substantial complaints of fatigue and hyperventilation, both to a similar degree. Physiological evidence of hyperventilation was found significantly more often in CFS patients than in healthy controls. However, no significant differences between CFS patients with and CFS patients without hyperventilation were found on severity of fatigue, impairment, number of complaints, activity level, psychopathology, and depression. It is concluded that hyperventilation in CFS should probably be regarded as an epiphenomenon.

Introduction

Chronic fatigue Syndrome (CFS) is defined as severe fatigue, lasting for at least six months, for which no somatic explanation can be offered. The pathogenesis of CFS is still unknown[1]. Because hyperventilation can produce substantial fatigue, and because fatigue is one of the main complaints in hyperventilation, it seems worthwhile to investigate their relationship. Grossman and de Swart[2] showed that 64% of the patients with hyperventilation syndrome complained of tiredness. In addition, the fatigue in hyperventilation[3] as well as in CFS[4-6] seems to be of a central type.

One might hypothesize that CFS is caused by hyperventilation. It is possible that stress causes hyperventilation, which in turn might lead to chronic fatigue. Another possibility is that hyperventilation plays a perpetuating role in CFS. Patients with CFS might develop hyperventilation due to their fatigue, and hyperventilation might in turn lead to an aggravation of fatigue.

Only a few studies have dealt with the relationship between CFS and hyperventilation. Rosen and colleagues[7] demonstrated hyperventilation in 38 of 40 patients suffering from CFS and claimed that hyperventilation plays an important role in the pathogenesis. Riley and colleagues[4], however, found no differences in the mean end-tidal PCO_2 both before and after exercise between 13 patients with CFS and 13 healthy controls. Saisch and colleagues[8] found evidence for hyperventilation in 9 of 31 CFS patients (29%). They did not find a relationship between the severity of hyperventilation and the degree of functional impairment, which was to be expected when hyperventilation would play a perpetuating role in CFS.

The first purpose of the present study is to determine whether there is any evidence for subjective complaints of hyperventilation in CFS, and whether there is evidence of fatigue in patients with hyperventilation. CFS patients and patients with known hyperventilation are compared to healthy controls to see whether these complaints are not only common but also specific for CFS and hyperventilation. The aim of the second part of the study is to determine whether there is any physiological evidence for hyperventilation in CFS and whether CFS patients show physiological evidence for hyperventilation more frequently than healthy controls. In the third part of the study, CFS patients with physiological evidence for hyperventilation (CFS HV) are compared to CFS patients without hyperventilation (CFS non-HV) on severity of fatigue, impairment, number of complaints, activity level, psychopathology, and depression, to determine the role of hyperventilation in CFS.

Method

Subjects

For the first part of this study, 39 patients with CFS and 32 healthy controls (all from a sample described elsewhere)[9] completed the questionnaires. The healthy controls were matched and recruited by a regional newspaper advertisement. Furthermore, 17 non-CFS patients with established hyperventilation (non-CFS HV) participated, all from the out-patient clinic of the Department of Pulmonology, Dekkerswald, University of Nijmegen. For the second and third part of the study 27 CFS patients and the 32 healthy controls from the first part of the study participated. The experimental groups are not of an equal size because the study was linked to an already ongoing study.

All CFS patients were diagnosed at the General Internal Medicine out-patient clinic of the University Hospital Nijmegen. CFS is defined as severe fatigue, lasting for at least six months, for which no somatic explanation can be offered. Patients were diagnosed with CFS if they fulfilled the Sharpe criteria[10]. According to these criteria, patients with a current diagnosis of major depression with melancholic or psychotic features, bipolar affective disorder, schizophrenia of any subtype, delusional disorders of any subtype, manic depressive illness, substance abuse, eating disorder, or proven organic brain disease (dementias of any subtype) were excluded.

Patients and healthy controls were diagnosed as having hyperventilation when they fulfilled three of the following criteria[11]:

- low $PaCO_2$ in rest (<4.5 kPa)
- High breathing frequency, irregular breathing, or frequent sighing in rest.
- Decreasing $PaCO_2$ in control condition on a spirometer.
- Inverted ventilators response to CO_2.
- Adding CO_2 results in a regulation of breathing.
- One of the following criteria during or after the provocation test:
  - no step change in $PetCO_2$ when stopping voluntary hyperventilation;
  - no step change in respiratory frequency when stopping voluntary hyperventilation;
  - $PaCO_2$ three minutes after the end of the provocation <90% of the starting level.

Instruments

Subjective fatigue was measured with the subscale of subjective fatigue of the Checklist of Individual Strength (CIS)[12]. On this scale, the minimum score is 1 and the maximum score is 7.

Level of impairment was assessed with the Sickness Impact Profile (SIP)[13]. This questionnaire measures the influence of complaints in different areas of daily functioning. For this study, eight subscales were used (alertness behaviour, sleep, homemaking, leisure activities, work, mobility, social interactions, ambulation).
Level of physical activity was assessed using an actometer. This apparatus is worn around the ankle for two weeks, recording the amount of movements every five minutes. This information is stored to an internal memory, and can be read by use of a personal computer[14].
Subjective complaints of hyperventilation were assessed by the Nijmegen Hyperventilation Questionnaire (NHQ)[15]. The cut-off score for hyperventilation is 23.
Psychopathology was measured with the Symptom Checklist (SCL-90), an indicator of psychological disturbances, and the Beck Depression Inventory (BDI)[16,17], a standardized self-report questionnaire for measuring depression.
Respiratory measurements were performed using a hyperventilation test in which the patient was connected to a closed spirometer circuit by a mouthpiece. A sampling capnograph measured PCO_2 in the respiratory air. Resting respiratory parameters were measured during five minutes: minute ventilators, $PetCO_2$, breathing frequency, irregularity of breathing, and the time course of $PetCO_2$ during the first five minutes of the test. Next, some CO_2 was given in the inspiratory air, to raise $PetCO_2$ by 1.0±0.2 kPa. The response of the ventilation to the increase in $PetCO_2$ was measured during another five minutes. Subsequently, the patient was disconnected from the spirometer, and only $PetCO_2$ was monitored during a one-minute period of voluntary hyperventilation, and during the three minutes thereafter. The patients were asked whether they recognized their daily symptoms, during the hyperventilation. Finally, an arterialised capillary blood gas sample was taken to assess a possible metabolic acidosis, compensating for chronic hyperventilation.

Statistical analysis

The analysis of differences between groups on dichotomous variables was carried out with the chi-square test. Bonferroni correction was applied for the comparison of three experimental groups. Assuming a significant level of 0.05, a difference was considered significant if the $p<0.017$. The analysis of differences between two groups on ratio variables was carried out with the t-test, with the significance level set at $p=0.05$. The analysis of differences between more than two groups on ratio variables was performed by analysis of variance. Multiple comparisons were made by Duncan's multiple range tests, with $p<0.05$.

Results

First part

The mean age of the CFS patients was 36.5 (sd=8.8), of the non-CFS patients with known hyperventilation (non-CFS HV) 44.0 (sd=12.6), and of the healthy controls 37.0 (sd=12.8). Only the non-CFS HV patients differed significantly in age from the other two groups. There were no significant differences in gender: 80% of the CFS patients were female, as were 59% of the non-CFS HV patients and 84% of the healthy controls.

Data concerning subjective complaints of hyperventilation and subjective complaints of fatigue are presented in table 1. On the NHQ, 59% of the CFS patients scored above the cut-off score for hyperventilation. This is significantly different from healthy controls (3%), but not from non-CFS HV patients (65%). Non-CFS HV patients had a mean CIS score for subjective fatigue of 5.2. This is significantly different from healthy controls (2.0), but not from CFS patients (5.9).

Table 1

MEAN SCORES (SD) ON SUBJECTIVE COMPLAINTS OF HYPERVENTILATION (NHQ), % ABOVE THE CUT-OFF SCORE FOR HYPERVENTILATION (NHQ>23), AND MEAN SCORE (SD) OF SUBJECTIVE FATIGUE (CIS), OF 39 CFS PATIENTS COMPARED TO 17 NON-CFS PATIENTS KNOWN WITH HYPERVENTILATION (NON-CFS HV), AND 32 HEALTHY CONTROLS

	CFS	non-CFS HV	Healthy
NHQ*	25.1 (9.8)	31.4 (11.6)	10.4 (6.3)
NHQ % > 23**	59%	65%	3%
CIS-subjective fatigue***	5.9 (1.1)	5.2 (2.2)	2.0 (1.1)

* One-way ANOVA, with Duncan multiple range test ($p<0.05$); CFS significantly different from non-CFS HV and healthy controls; non-CFS HV significantly different from healthy controls

** Chi-square ($p<0.001$); CFS significantly different from healthy controls ($p<0.001$); non-CFS HV significantly different from healthy controls ($p<0.001$); non-CFS HV not significantly different from CFS

*** One-way ANOVA, with Duncan multiple range test ($p<0.05$); CFS significantly different from healthy controls; non-CFS HV significantly different from healthy controls; non-CFS HV not significantly different from CFS

Second part

The CFS patients and the healthy controls who underwent respiratory measurements did not differ significantly on age and gender. Mean age of the CFS patients was 36.6 (sd=8.0), and of the healthy controls 37.0 (sd=12.8). Seventy-eight percent of the CFS patients were female, compared

to 85% of the healthy controls. Between CFS patients and healthy controls significant differences were found on fatigue, impairment, number of complaints, level of activity, subjective complaints of hyperventilation, and psychopathology, as expected[9] (table 2). Table 3 shows the results of the respiratory measurements in CFS and healthy controls. Significantly more CFS patients showed hyperventilation (59%) than did healthy controls (22%). CFS patients differed from healthy controls on $PetCO_2$ and recognition of complaints, but not on the other respiratory parameters.

Table 2

MEAN SCORES (SD) OF 27 CFS PATIENTS AND 32 HEALTHY CONTROLS RECRUITED FOR RESPIRATORY MEASUREMENTS, ON SUBJECTIVE FATIGUE (CIS), IMPAIRMENT (SIP), NUMBER OF COMPLAINTS, ACTIVITY LEVEL (ACTOMETER), SUBJECTIVE COMPLAINTS OF HYPERVENTILATION (NHQ), PSYCHOPATHOLOGY (SCL-90) AND DEPRESSION (BDI)

	CFS	Healthy	p - value*
CIS-subjective fatigue	5.9 (1.0)	2.0 (1.1)	<0.001
SIP	17.1 (6.3)	1.2 (0.3)	<0.001
Number of complaints	7.4 (3.7)	0.0 (0.0)	<0.001
Actometer	25.1 (12.3)	36.4 (12.2)	<0.001
NHQ	25.6 (11.3)	10.4 (6.3)	<0.001
SCL-90	155.4 (27.2)	106.9 (22.0)	<0.001
BDI	10.6 (5.3)	2.7 (4.0)	<0.001

* Using the t-test

Third part

The 16 CFS patients with hyperventilation (CFS HV) and the 11 CFS patients without hyperventilation (CFS non-HV) were compared on subjective fatigue (CIS), impairment (SIP), number of complaints, activity level (actometer), subjective complaints specific for hyperventilation (NHQ score), psychopathology (SCL-90) and depression (BDI). No significant differences between groups were found (table 4). CFS HV patients as well as CFS non-HV patients were both extremely fatigued and impaired. There was neither a significant difference in the number of complaints, nor the level of activity or subjective complaints of hyperventilation. Finally, CFS HV patients and CFS non-HV patients did not differ on psychopathology and depression.

Table 3

MEAN SCORES (SD) OR % ON RESPIRATORY MEASUREMENTS IN 27 CFS PATIENTS AND 32 HEALTHY CONTROLS

	CFS	Healthy	p - value
$PetCO_2$ (kPa)*	4.5 (0.66)	4.9 (0.40)	<0.005
$PetCO_2$ < 4.5**	52%	22%	<0.05
$PaCO_2$ *	4.75 (0.69)	4.83 (0.57)	NS
Breathing frequency*	13.1 (3.7)	15.1 (3.7)	NS
Tidal volume*	0.604 (0.20)	0.560 (0.18)	NS
Decreasing $PetCO_2$**	36%	22%	NS
Irregular breathing**	30%	16%	NS
Delayed recovery after provocation**	56%	38%	NS
Recognition**			<0.01
none	41%	81%	
partly	37%	13%	
completely	22%	6%	
Hyperventilation, according to physiological criteria**	59%	22%	<0.005

* Using the t-test
** Using chi-square

Table 4

MEAN SCORES (SD) OF 16 CFS PATIENTS WITH HYPERVENTILATION (CFS HV) AND 11 CFS PATIENTS WITHOUT HYPERVENTILATION (CFS NON-HV) ON SUBJECTIVE FATIGUE (CIS), IMPAIRMENT (SIP), NUMBER OF COMPLAINTS, ACTIVITY LEVEL (ACTOMETER), SUBJECTIVE COMPLAINTS OF HYPERVENTILATION (NHQ), PSYCHOPATHOLOGY (SCL-90) AND DEPRESSION (BDI)

	CFS HV	CFS non-HV	p - value*
CIS-subjective fatigue	5.8 (1.0)	6.0 (0.9)	NS
SIP-score	18.2 (6.1)	16.4 (6.5)	NS
Number of complaints	8.1 (3.6)	6.5 (3.7)	NS
Actometer	24.1 (10.2)	26.6 (15.2)	NS
NHQ	25.6 (8.2)	25.5 (15.4)	NS
SCL-90	153.9 (28.1)	157.9 (27.1)	NS
BDI	10.1 (4.0)	11.4 (6.9)	NS

* Using the t-test

Discussion

Patients with CFS endorsed subjective complaints of hyperventilation, similar to non-CFS patients with known hyperventilation. The latter showed substantial fatigue, of similar severity as CFS patients. Physiological evidence for hyperventilation was found significantly more often in CFS patients (59%) than in healthy controls (22%), with a significant difference in the mean resting $PetCO_2$. Rosen and colleagues[7] found hyperventilation in 93% of the CFS patients and 55% of the healthy controls, whereas Saisch and colleagues[8] found evidence for hyperventilation in 29% of the CFS patients, and Riley and colleagues[4] found no differences in the mean $PetCO_2$ between CFS patients and healthy controls. These conflicting findings can he explained by the differences in the criteria used in diagnosing hyperventilation. In the study by Rosen and colleagues[7], less stringent criteria were used. Patients were also diagnosed with hyperventilation if they had a positive 'think test': three minutes after the hyperventilation provocation test, patients were requested to close their eyes and think about the circumstances of an attack and the feelings and sensations experienced. A fall of end-tidal $PaCO_2$ of 1.3 kPa or more was taken as a positive response[18]. However, the resting $PetCO_2$ in that study did not differ between CFS patients and healthy controls, as in the study of Riley and colleagues[4]. In the study by Saisch and colleagues[8], the criteria were more strict than in our study. Patients were diagnosed with hyperventilation only if the $PetCO_2$ was less than 4.0 kPa at rest, during or after exercise, or at five minutes after the end of voluntary overbreathing. Using the criterion of a $PetCO_2$ of less than 4.0 kPa, in our study, 19% of the CFS patients and none of the healthy controls were diagnosed with hyperventilation. This is closer to the finding of 29% hyperventilating CFS patients found in the study by Saisch and colleagues[8].

If hyperventilation plays an important role in the pathogenesis or perpetuation of CFS, one would assume that hyperventilation is common in CFS, and one would expect higher scores of fatigue and impairment in the CFS patients with hyperventilation, compared to the CFS patients without hyperventilation. Like Saisch and colleagues[8], we found physiological evidence for hyperventilation in some of the CFS patients, the exact percentage depending on the criteria used. In addition, we could show that the high percentage of 93% found in the study by Rosen and colleagues[7] could be explained by the less strict criteria used: hyperventilation in CFS is not as common as they suggest. Comparing CFS patients with hyperventilation to CFS patients without hyperventilation, no differences on fatigue and impairment were found, as in the study by Saisch and colleagues[8]. There were also no differences found on variables such as the number of complaints, level of activity, psychopathology, and depression. If hyperventilation plays a role

in CFS, one would at least expect some differences. Using the strict criteria of a 4.0 kPa $PaCO_2$ at rest, five of our CFS patients showed hyperventilation. However, even then, no differences are found between CFS patients with and CFS patients without hyperventilation. Therefore, it is unlikely that hyperventilation plays a role in the pathogenesis or perpetuation of CFS.

Depending on the criteria one uses, it can be said that signs of hyperventilation were found in a substantial number of the CFS patients. Furthermore, non-CFS hyperventilating patients had significantly more complaints of fatigue than healthy controls. However, we did not find more complaints of fatigue in hyperventilating CFS patients than in non-hyperventilating CFS patients. Therefore, hyperventilation is probably an epiphenomenon in CFS, and does not play a substantial causal or perpetuating role.

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Is physical deconditioning a perpetuating factor in chronic fatigue syndrome?

4

A CONTROLLED STUDY ON MAXIMAL EXERCISE PERFORMANCE AND RELATIONS WITH FATIGUE, IMPAIRMENT AND PHYSICAL ACTIVITY

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Abstract

Background. Chronic fatigue syndrome (CFS) patients often complain that physical exertion produces an increase of complaints, leading to a greater need for rest and more time spent in bed. It has been suggested that this is due to a bad physical fitness and that physical deconditioning is a perpetuating factor in CFS. Until now, studies on physical deconditioning in CFS have shown inconsistent results.

Methods. Twenty CFS patients and 20 matched neighbourhood controls performed a maximal exercise test with incremental load. Heart rate, blood pressure, respiratory tidal volume, O_2 saturation, O_2 consumption, CO_2 production, and blood-gas values of arterialized capillary blood were measured. Physical fitness was quantified as the difference between the actual and predicted ratios of maximal workload versus increase of heart rate. Fatigue, impairment and physical activity were assessed to study its relationship with physical fitness.

Results. There were no statistically significant differences in physical fitness between CFS patients and their controls. Nine CFS patients had a better fitness than their control. A negative relationship between physical fitness and fatigue was found in both groups. For CFS patients a negative correlation between fitness and impairment and a positive correlation between fitness and physical activity was found as well. Finally, it was found that more CFS patients than controls did not achieve a physiological limitation at maximal exercise.

Conclusion. Physical deconditioning does not seem a perpetuating factor in CFS.

Introduction

Chronic fatigue syndrome (CFS) is defined as a severe fatigue lasting for at least 6 months, for which no somatic explanation can be offered and which leads to severe disability in daily life. CFS patients often complain that physical exertion produces an increase in complaints, leading to a greater need for rest and more time spent in bed. In some CFS studies it has been argued that muscle deficits might cause this fatigue after activity[1-3]. More recent studies on physical exercise in CFS showed that the neuromuscular mechanism is intact[4-9]. Wessely and colleagues[10] hypothesized that physical deconditioning might play an important role in CFS. The rationale was that because CFS patients experience a worsening of complaints after activity, they learn to avoid activity in order to prevent an increase of complaints. Being inactive, however, results in a decrease of physical fitness. This means that over time complaints get worse at an increasingly lower level of physical activity. In this way a vicious and perpetuating circle might be established, resulting in a decreasing physical fitness. Based on this hypothesis, the role of (avoidance of) physical activity in CFS has been emphasized more and more[11]. In cognitive behavioural therapy[12,13] as well as in graded exercise therapy[14] a gradually increasing activity programme is of main importance. One might wonder, however, whether improving physical fitness is an essential factor in CFS, or whether other factors determine treatment effects. If physical fitness is an important and perpetuating factor in CFS, one would not only expect CFS patients to have a worse physical fitness, but one would also expect a negative relationship between physical fitness and fatigue and impairment and a positive relationship between physical fitness and physical activity.

Studies on aerobic or cardiocirculatory deconditioning in CFS have shown contradictory results[15-20]. These differences might be due to differences in tests, sample sizes and patient and control selection. Differences in tests used make it difficult to compare results. However, the most important reason for the inconsistencies found seems to be the use of an inappropriate control group in most studies. Physical fitness in CFS should not be compared with selected healthy and rather active controls. To deal with this problem, Sisto and colleagues[18] used sedentary controls. In our study, well-matched neighbourhood controls are used. Although inconsistencies exist in the findings concerning physical fitness, most studies are consistent in their findings that at least part of the CFS patient sample does not attain a physiological limitation on a maximal exercise test. The aims of the present study are to determine whether CFS patients have a worse physical fitness as compared to matched neighbourhood controls, and whether there is a negative relationship between physical fitness and fatigue and impairment and a positive relationship between physical fitness and physical activity. We also investigated whether CFS patients attain a physiological maximum on a maximal exercise test.

Method

Subjects

Patients diagnosed at the General Internal Medicine out-patient clinic of the University Hospital Nijmegen, who already agreed to participate in scientific studies, were asked to participate. Patients were diagnosed as having CFS if they fulfilled the Fukuda criteria[21]. In addition, CFS patients were only included if they had a CIS fatigue severity score of ≥40 and a total score on the eight SIP subscales used of >800, to guarantee severe fatigue and disability (see instruments)[22]. Patients invited for the current study were further selected on whether they lived in the surroundings of our hospital, because a heart rate monitor was brought to the patients' and controls' home a day before the exercise test and was picked up again one day after the test. None of the patients refused. All patients were asked to invite a neighbour of the same gender and about the same age as a control person. Twenty of 26 CFS patients fulfilled our additional criteria of the CIS and the SIP and found a neighbourhood control of about the same age and the same sex. So 20 CFS patients and 20 matched neighbourhood controls participated.

Instruments

Fatigue

Fatigue was measured by the subscale fatigue severity of the fatigue questionnaire Checklist Individual Strength (CIS)[22]. This scale consists of eight items concerning fatigue during the last two weeks. Each item is scored on a 7-point Likert scale, so the range is 8 - 56.

Functional impairment

The Sickness Impact Profile (SIP)[23,24] was used to assess functional impairment. This questionnaire measures the influence of complaints in different areas of daily functioning. Eight subscales were used (alertness behaviour, sleep, homemaking, leisure activities, work, mobility, social interactions and ambulation).

Physical activity

This was measured using the actometer[25]. The actometer is an apparatus worn around the ankle for two weeks, recording the amount of movements every five minutes. The actometer consists of a piezoelectric sensor. Acceleration of the sensor results in an output signal. This information is stored to an internal memory, and can be read by use of a personal computer. The mean

actometer score for the days that the actometer was worn before the exercise test was used to assess the level of physical activity.

Exercise test

A bicycle ergometer test with incremental load was used as an exercise test. The workload was increased every minute in steps of 10% of estimated maximal workload, in order to complete the maximal exercise test in approximately 10 minutes[26]. The steps varied from 10 to 30 watt/minute. Subjects were instructed to go on until they could no longer continue. They were verbally encouraged to perform maximally. During this test, heart rate, blood pressure, respiratory tidal volume, O_2 saturation, O_2 consumption, CO_2 production, and bloodgas values of arterialized capillary blood (before and after exercise, at minute three, six, and nine of the exercise and at maximal workload) were measured. Every three minutes and at maximal workload, the modified Borgscale was used to assess the rate of perceived exertion[27]. On a scale from 1 to 10, patients were asked to indicate how difficult it was to perform the pedalling exercise. The intensity of anaerobic workload was measured from the difference in base excess at rest and three minutes after maximal workload, which represents the produced lactate within the cells of the leg muscles. Achieved maximal workload (W) was compared with the predicted value. The predicted maximal workload was calculated from[28]:

$$Wmax\_pred = \frac{VO_2max\_pred - VO_2rest\_pred}{10.29}$$

In this formula, predicted maximal ventilatory O_2 uptake (VO_2max_pred) is related to height (H/cm), age (A/year) and sex (S/m=0, f=1)[29] :

$$VO_2max\_pred\ (l/minute) = 0.046H - 0.021A - 0.62S - 4.31$$

and[30]

$$VO_2rest\_pred = 0.25\ l/minute.$$

Maximal heart rate (HR) was compared with the predicted maximal heart rate, depending on age (A/year)[28]:

$$HRmax\_pred\ (beats/minute) = 220 - A.$$

Fitness was defined as the differences in slope of the relationships between heart rate and external workload of the individual subject versus a normalized slope. Fit subjects have relatively low heart rates at a certain workload and vice versa[31]. In formula:

$$\frac{Wmax}{HRmax - HRrest} - \frac{Wmax\_pred}{HRmax\_pred - HRrest} = \text{Watt per beat.}$$

A negative outcome indicates a fitness that is worse than would be expected; a positive outcome indicates a better fitness than expected.
Subjects were considered attaining a physiological limitation if one of the following criteria was met: 1) attainment of predicted maximal heart rate; 2) increase of base excess at three minutes after maximal workload compared with base excess at rest (lactate production) of more than 10 mmol/minute; 3) increase of CO_2 pressure in blood at maximal workload compared with the value at rest.

The 24 hours heart rate

This was assessed using a Polar sport tester. The Polar sport tester consists of a belt around the chest, containing ECG electrodes, amplifier and transmitter, and a watch. The ECG signals are sent to the watch, recording the R-tops in an internal memory every 60 seconds, during 24 hours. For the analysis in this study mean scores of every half an hour were used. The Polar sport tester was brought to the patients' and controls' home to wear during the 12 hours preceding the start of the ergometer test. After the ergometer test the Polar sport tester was worn for another 12 hours. Then the sport tester was collected from the subjects' homes.
For six controls and four CFS patients almost all data of the Polar sport testers were missing, probably because of pressing the buttons accidentally during sleep. Also, 10 subjects (one CFS patient and nine controls) had incidental missing data. In these cases (1.7% of all sport tester data) missing values were replaced by the mean value of the half hour scores before and after the missing value of the particular subject.

Statistical analysis

Differences between groups were tested using one-way analysis of variance (ANOVA) or repeated measures ANOVA for ratio variables. The Mann-Whitney U test was used in case of skewed variables, chi-square was used for dichotomous variables. Fisher's Exact Test was used when >20% of the cells had an expected count <5. Before Pearson correlation coefficients were computed, skewed variables were transformed. To test whether the correlations obtained for CFS and for controls were significantly different, both correlations were converted to Fisher's z and the difference between them was divided by the standard error of the difference to yield a normal curve deviate (z)[32]. For all tests, the significance level was set at $p<0.05$.

Results

Patient and control characteristics

Demographic data, height, weight, fatigue severity, functional impairment and physical activity are displayed in table 1. There were no significant differences in gender, age, height and weight. On fatigue severity, functional impairment and physical activity differences were found as expected. Mean duration of complaints in CFS was 3.2 years (±2.5).

Table 1

CHARACTERISTICS (% OR MEAN (SD)) OF CFS PATIENTS (N=20) AND CONTROLS (N=20)

	CFS	Controls	p - value
Female (%)	60	60	1.00
Age (yrs)	34.1 (8.3)	32.8 (7.2)	0.59
Height (cm)	175.7 (9.4)	174.8 (9.5)	0.78
Weight (kg)	72.0 (16.4)	71.5 (14.2)	0.91
Fatigue (CIS; range 8-56)	51.7 (5.1)	13.4 (5.1)	<0.001*
Functional impairment (SIP-8)	1743 (1249-2058)	0 (0-0)	<0.001*
Physical activity (actometer)[a]	58.2 (27.2)	99.5 (25.0)	<0.001*

Chi-square for % female; Mann-Whitney U test for SIP, medians (25th and 75th percentile) presented; one-way ANOVA for other variables

[a] Deviating N because of failing actometers, N=15 for CFS and N=18 for controls

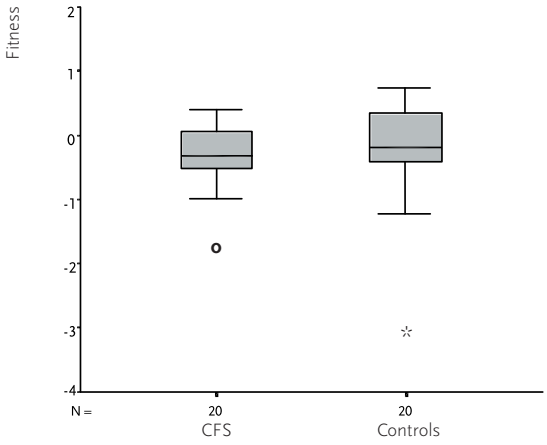
* p<0.05

Fitness

CFS patients had a mean fitness of –0.32 ± 0.50 watts/beat and their controls had a mean fitness of –0.22 ± 0.82 watts/beat (non-significant: Mann-Whitney U test, p=0.25). Nine of the 20 CFS patients had a better fitness than their own control. In Figure 1 a boxplot of fitness in CFS and controls is displayed.

Figure 1

BOXPLOT OF FITNESS FOR CFS AND CONTROLS

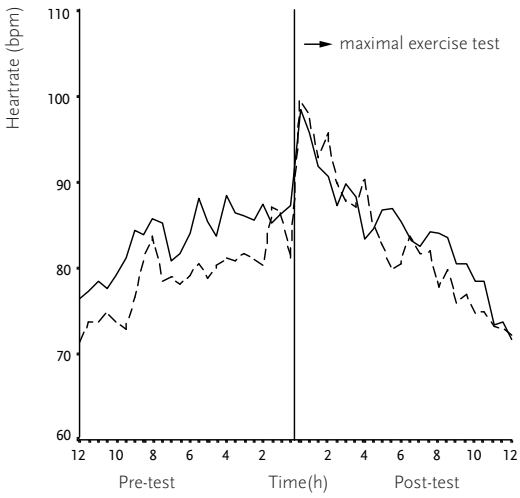


box is 25th to 75th percentile (interquartile range, IQR), line in box is median, lines above and under the box are 1.5 times above 25th and under 75th percentile respectively,

o is an outlier
(between 1.5 IQR and 3 IQR from box)
✲ is an extreme
(more than 3 IQR from box)

Figure 2

HEART RATE 12 HOURS BEFORE UP TO 12 HOURS AFTER THE MAXIMAL EXERCISE TEST, CFS PATIENTS COMPARED TO CONTROLS



Repeated measures ANOVA: within subjects, p<0.001 (F=9.66; df=47); interaction effect, p=0.75 (F=0.85; df=47)

CFS (N=16)
Controls (N=14)

Heart rate

Heart rates from 12 hours before the test up to 12 hours after the test for CFS and their controls are displayed in figure 2. No significant interaction effect was found.

Table 2

OXYGEN CONSUMPTION AND CO_2 PRODUCTION (SD) IN REST AND AT MAXIMAL WORKLOAD FOR CFS (N=20) AND CONTROLS (N=20)

	Rest	Maximal workload	Within subjects p-value	Interaction effect p-value
O_2 consumption (l/minute)				
CFS	0.30 (0.08)	2.01 (0.74)	<0.001*	0.22
Controls	0.29 (0.08)	2.27 (0.68)	(F=288.95; DF=1)	(F=1.58; DF=1)
CO_2 production (l/minute)				
CFS	0.27 (0.09)	2.37 (0.90)	<0.001*	0.20
Controls	0.28 (0.09)	2.75 (0.90)	(F=270.96; DF=1)	(F=1.72; DF=1)
O_2 pressure in blood (kPa)				
CFS	9.07 (1.05)	11.29 (1.34)	<0.001*	0.10
Controls	8.87 (0.92)	10.25 (1.01)	(F=50.19; DF=1)	(F=2.84; DF=1)
CO_2 pressure in blood (kPa)				
CFS	5.19 (0.51)	4.65 (0.57)	<0.001*	0.03*
Controls	5.36 (0.46)	5.22 (0.59)	(F=14.42; DF=1)	(F=4.89; DF=1)

Repeated measures ANOVA
* p<0.05

Oxygen consumption and CO_2 production

Table 2 shows the O_2 and CO_2 uptake and production. CO_2 pressure in the blood declined more for CFS than for controls (p=0.03). There were no other significant interaction effects for the respiratory exchange variables.

Fitness and relations with fatigue, impairment and physical activity

For CFS as well as for controls a significant correlation of –0.45 was found between fitness and fatigue (p=0.049 and 0.044 respectively). In CFS significant correlations between fitness and functional impairment (r=0.49, p=0.027) and fitness and physical activity (r=0.54, p=0.039; N=15 because of failing actometers) were found as well. Because 85% of the controls had a functional impairment score of zero, a correlation between functional impairment and fitness could not be computed. The correlation between fitness and physical activity in controls was non-significant (r=0.28, p=0.260; N=18 because of failing actometers). The difference in the correlations between fitness and physical activity in CFS and in controls (0.54 and 0.28 respectively) were statistically non-significant (p=0.414).

Exercise capacity

Neither the duration of the maximal bicycle ergometer test nor achieved workloads were significantly different for CFS and controls (table 3). However, there was a statistically significant difference for the percentage of the predicted workload reached, being lower in CFS. On average, CFS patients reached 70% of their predicted workload, whereas the controls reached 83% of their predicted value. For heart rate scores during exercise, no statistically significant differences were found.

Attaining a physiological limitation

Of the CFS patients 55% performed up to a physiological limitation, compared with 80% of the controls (this difference was not significant, table 4).

Perceived exertion

Not all subjects performed the maximal exercise test for six minutes or more. Therefore, Borgscale scores were compared three minutes after starting the test and at maximal workload only. Scores on the Borgscale three minutes after starting the test were 3.82±0.88 for CFS (N=17) and 2.44±0.86 for controls (N=18). At maximal workload Borgscale scores were 8.76±1.68 for CFS and 7.33±2.11 for controls. There was a significant within subjects' effect ($p<0.001$; $F=210.06$; $df=1$). No significant interaction effect was found ($p=0.94$; $F=0.01$; $df=1$).

Table 3

EXERCISE CAPACITY (MEAN AND (SD)) FOR CFS PATIENTS (N=20) AND CONTROLS (N=20)

	CFS	Controls	p-value
Time (minutes)	8.0 (2.3)	9.2 (1.9)	0.07
Workload (watt)			
predicted value	241 (51.5)	245 (50.1)	0.81
value reached	172 (68.3)	204 (64.1)	0.14
% of the predicted value reached [a]	70 (17)	83 (18)	0.02*
Heart rate (bmp)			
predicted value	186 (8.3)	187 (7.2)	0.59
value reached	165 (16.2)	173 (13.4)	0.08
% of the predicted value reached [a]	89 (8)	92 (7)	0.11

One-way ANOVA

a Value reached / predicted value x 100

* $p<0.05$

Table 4

PERCENTAGE (N) OF CFS PATIENTS (N=20) AND CONTROLS (N=20) ATTAINING A PHYSIOLOGICAL LIMITATION AT MAXIMAL EXERCISE

	CFS	Controls	p-value
ΔHR >0 [a]	5 (1)	15 (3)	0.61
ΔBE >10 [b]	35 (7)	55 (11)	0.20
$\Delta PaCO_2$ >0 [c]	30 (6)	40 (8)	0.51
Attaining one of these criteria	55 (11)	80 (16)	0.09

Fisher's exact test for ΔHR; chi-square for other variables

a ΔHR, heart rate at maximal workload - predicted heart rate

b ΔBE, base excess at maximal workload - base excess 3 minutes after test

c $\Delta PaCO_2$, CO_2 pressure in blood at maximal workload - CO_2 pressure in blood at rest

Discussion

In the present study CFS patients did not have a worse physical fitness compared with their controls. Both groups had a lower physical fitness than would be expected according to height, age and sex. This particularly emphasizes the importance of a well-matched control group. In our study, the fitness score of one of the controls was an extreme. When this extreme is excluded from the analysis, the difference remains statistically non-significant. One might suggest that not finding a significant difference in fitness is due to a power problem, because of sample sizes. However, almost half of the CFS patients had a better fitness than their own control. This result underlines the conclusion that there is no difference in fitness between CFS patients and their controls. Our finding agrees with that of Sisto and colleagues[18], who found that CFS patients had a low but normal fitness, comparable to sedentary controls. Another objection might be that in spite of substantial and expected differences in fatigue, functional impairment and level of activity, only a selected group of patients was included. Bedridden patients, in particular, are unlikely to participate in these scientific studies. Van der Werf and colleagues[33] recently found that passive patients can be distinguished from the relatively active patients based on the actometer. In the present study three passive CFS patients participated. These patients resemble bedridden patients.

Concerning respiratory variables it was found that the CO_2 pressure in the blood of CFS patients decreased more than in the controls. This might indicate that CFS patients tend to hyperventilate during exercise. In other studies[34-35] it was found that hyperventilation, although prevalent in a substantial part of the cases, does not seem to play an essential role in CFS. However, no other significant differences were found concerning oxygen consumption and carbon dioxide production. In addition, according to Wasserman and colleagues[28] oxygen consumption should be 10.29 (±1) ml per minute per watt for normal subjects. If we compute millilitre oxygen consumption per minute per watt for the subjects in our study (O_2 consumption at maximal workload minus O_2 consumption at rest multiplied by 1000 and divided by maximal workload reached) this is 9.94 (±1.31) for CFS patients and 9.71 (±1.41) for controls. These values are both very similar to the normal value of Wasserman and colleagues[28]. Very unfit subjects usually need more O_2 per watt. Consequently, this finding adds to the conclusion that the fitness of the CFS patients is not substantially impaired.

The maximal workload reached during an incremental bicycle ergometer test did not differ between CFS patients and controls, neither did the heart rate at maximal workload. However, the average percentage of the predicted maximal workload reached was lower for CFS than for

controls. In spite of the absence of significant differences in physical fitness, CFS patients are not performing until they are limited by physiological mechanisms. It might be supposed that achieved workload is a parallel test for physical activity. Indeed, post hoc analysis revealed that the average percentage of the predicted maximal workload reached is highly correlated with physical activity in CFS ($r=0.78$, $p<0.001$), but not in controls ($r=0.16$, $p=0.55$). These correlations are significantly different ($p=0.03$).

Because there was no significant difference in fitness between CFS and controls, it is not likely that physical fitness should be considered a perpetuating factor in CFS. The relationship between physical fitness and fatigue is of less importance now. Nevertheless, the fact that the relationship between physical fitness and fatigue is of the same strength for both groups, indicates that a worse physical fitness goes with more fatigue for all subjects, for which CFS patients are no exception. The finding that in CFS a worse fitness goes together with a lower level of physical activity (and higher level of impairment), is of interest. For controls no relationship between fitness and physical activity was found. Apparently, CFS patients with a lower physical fitness are less active, whereas controls are not. It is conceivable that CFS patients with a lower physical fitness adjust to this by being less active, while controls do not. However, although the correlations between fitness and the level of activity are different in CFS and in controls this difference is not statistically significant. Besides, the sample sizes were small. Therefore, this finding has to be interpreted with caution. Wagenmakers[11], reviewing some of the literature on physical fitness and CFS, concludes that deconditioning might be a perpetuating factor. In this article it is supposed that CFS patients show a metabolic adaptation to a low level of physical activity. Wagenmakers[11] suggests that the abnormal physiology found in CFS may well be a consequence of the lack of exercise in CFS patients. For this reason he suggests that exercise programmes have to be brought into practice. However, this explanation does not seem plausible: in our study the controls also had a lower physical fitness than predicted while they were not less active or fatigued. Considering the above mentioned correlations as well, it seems more likely that low levels of activity are an adaptation to a lower physical fitness of some CFS patients but not for controls, rather than that low levels of activity lead to a worse physical fitness. Besides, Fulcher & White[14] showed that there was no relationship between improvement in CFS after an exercise treatment programme and increase of peak aerobic capacity produced by exercise after this programme. This finding adds to the hypothesis that factors other than physical fitness determine a lower level of activity, fatigue and impairment in CFS. Possibly cognitions are responsible for a lower exercise tolerance in some CFS patients. Vercoulen and colleagues[25] found that low levels of physical activity are in part caused by attributing complaints to a physical cause. Petrie and colleagues[36] found that CFS patients who expected that activity would have negative consequences for their complaints, were also more impaired. However, based on the results of our study, it must be concluded that a worse physical fitness does not seem to be a perpetuating factor in CFS.

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Impact of a maximal exercise test on symptoms and activity in chronic fatigue syndrome

5

Submitted

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Abstract

Objective. This study examined the effects of exercise on symptoms and activity in CFS.
Methods. Twenty CFS patients and 20 neighbourhood controls performed an incremental exercise test until exhaustion. Fatigue, muscle pain, minutes spent resting and the level of physical activity were assessed with a self-observation list. Physical activity was assessed with an actometer as well. Data were obtained three days before the maximal exercise test up to five days thereafter.
Results. For CFS patients daily observed fatigue was increased up to two days after the exercise test. For controls self-observed fatigue returned to baseline after two hours. Both CFS patients and controls spent more minutes resting on the day before and on the day after the maximal exercise test. For CFS patients self-observed minutes resting was increased on the day of the exercise test also. For neither group a decrease of actometer recorded or self-observed physical activity after exercise was found.
Conclusion. Fatigue in CFS patients increased after exercise but the level of actual physical activity remained unchanged.

Introduction

Chronic Fatigue Syndrome (CFS) is characterized by a severe, disabling and unexplained fatigue, lasting for at least six months. CFS patients often report that even minimal exercise aggravates symptoms and leads to a decrease of physical activity[1]. Nevertheless, in several studies gradually increasing activity programs have proven to be important in the treatment of CFS[2-7]. Although CFS patients seem to have the belief that activity is harmful, the effect of exercise on symptoms and activity in CFS patients is not known.

Until now only a few studies examined exacerbation of symptoms and decrease of physical activity after exercise. Most of these studies mainly concern physiological responses to treadmill or cycle exercise tests in CFS. Two uncontrolled studies, one measuring on the seventh day after exercise[8], and one every day up to 7 days[9], did not find any adverse effects of exercise on symptoms and activity. Conversely, two controlled studies did find an increase of fatigue after exercise. One study measured after 24 hours[10], one up to 4 days[11].

In the studies mentioned, assessment took place by just asking for adverse after-effects following testing[8], by questionnaires like the modified version of the Profile Of Mood Scales (POMS)[9-11], an activity restriction index[9], a symptom log[9], and daily ratings of fatigue[11]. Only in one study an accelerometer was used to measure the effect of exercise on physical activity. An unexplained reduction in activity on the fifth day after the exercise test was found for CFS but not for controls[12].

It has been shown that self-report questionnaires on physical activity do not correlate very well with accelerometer readings[13]. Whereas questionnaires that require simple ratings of actual activity were related to the accelerometer, instruments that require general subjective interpretations of activity were not. Furthermore, questionnaires like the POMS do not seem sensitive for day-to-day changes in repeated measurements. Standardized self-observation measures seem more appropriate to assess fluctuations in fatigue[14,15].

The purpose of the current study was to investigate the effect of a maximal exercise test (MET) on fatigue, muscle pain, rest and activity on the days surrounding the exercise test. In a former study[16] the physiological aspects of a maximal exercise test in CFS compared to controls were described. No significant differences in physical fitness between CFS patients and their controls were found. In this same study self-observation measurements as well as an accelerometer were used. These results are presented now. Symptoms and activity were measured the hours before and after the test, as well as the days before, of and after the exercise test. CFS patients were compared with neighbourhood controls. It was expected that

after the MET for CFS patients as well as for controls fatigue, muscle pain and rest will be increased and physical activity will be decreased as compared with baseline. In this context, a significant difference in the extent as well as in the duration of changes in symptoms and activity between CFS and controls was anticipated. CFS patients were expected to experience a more severe increase of symptoms, of longer duration, and a more prevalent and longer lasting decrease of activity.

Methods

Subjects

Patients were recruited from a group of CFS patients diagnosed at the General Internal Medicine outpatient clinic of the University Medical Centre Nijmegen, a national referral expert centre for CFS. The diagnosis CFS was made after a thorough medical investigation. All patients fulfilled the Fukuda criteria for CFS[17].

As a rule, screening questionnaires were sent to all patients at the outpatient clinic diagnosed with CFS. For the present study only CFS patients with a CIS fatigue severity score of 40 or more, and a total score of the SIP-8 of more than 800 were included to guarantee severe fatigue and disability (see instruments)[18]. With these operational criteria severe fatigue and impairment in CFS can be distinguished from fatigue and impairment in other conditions[18]. Finally, patients had to be able to recruit a neighbour of the same gender and about the same age, as a control. Twenty-six CFS patients, living in the surroundings of our hospital, were asked to participate. Twenty of these met our additional CIS and SIP-8 criteria and found a neighbourhood control. Prior to their commitment, all subjects were completely informed about the method and procedure of the study. Physiological characteristics of these subjects have been described in detail elsewhere[16].

Measures

Checklist Individual Strength

The subscale fatigue severity of the fatigue questionnaire Checklist Individual Strength (CIS)[18] was used to assess overall fatigue. The subscale fatigue consists of 8 items asking for fatigue severity during the last two weeks. Each item was scored on a 7-point Likert scale, so the range is 8-56. Cronbach's alpha is 0.88. This subscale has proved its usefulness in several studies, and, for instance, distinguishes fatigue in CFS patients from fatigue in patients with functional bowel disorder and healthy controls[18].

Sickness Impact Profile

Functional impairment was assessed using the Sickness Impact Profile (SIP)[19,20]. This questionnaire measures the influence of complaints in different areas of daily functioning. The following eight subscales were used: alertness behaviour, sleep, homemaking, leisure activities, work, mobility, social interactions and ambulation. The sum of the weights of items of these subscales is referred to as the SIP-8. These subscales of the SIP are often used in CFS and distinguish functional impairment in CFS patients from patients with several other physical complaints[18].

Maximal exercise test

A bicycle ergometertest with incremental load was used as an exercise test[21]. The workload was increased every minute in steps of 10% of estimated maximal workload in order to complete all maximal exercise tests (MET) in approximately 10 minutes. Steps varied from 10 to 30 Watt per minute. Subjects were verbally encouraged to perform maximally until exhaustion. The time spent on the bicycle ergometer was 8.0±2.3 minutes for CFS and 9.2±1.9 minutes for controls. The percentage of the predicted maximal workload reached, (value reached / predicted value) x 100, was 83% for controls and 70% for CFS.

Self observation

A self-observation list was used to assess fatigue, muscle pain and activity from three days before up to five days after the MET.

Daily assessment

Except for the day before, the day of and the day after the MET, self-observation scores were obtained at breakfast, lunch, dinner and bed time, with 9 a.m., noon, 6 p.m. and 10 p.m. as a directive, on a scale from 0 to 4. For daily observed fatigue and daily observed muscle pain, 0 meant 'no symptoms' and 4 meant 'very severe symptoms'. For daily observed activity, 0 meant 'not active at all' and 4 'very active'. Scores were added up for each day and divided by four, resulting in a score from 0 to 4 for daily observed fatigue, daily observed muscle pain and daily observed activity. In addition, every day the time spent resting was asked for. Daily observed rest was defined as the number of minutes rest during a day. The scores for the daily data the day before, the day of and the day after the MET were obtained as averages of the hourly scores. For daily observed fatigue, muscle pain and activity, only the data obtained after performing the MET were used to compute the mean of the day the MET was performed.

Hourly assessment

The day before, the day after, and the day of the MET, assessments of fatigue, muscle pain, and activity were made every hour to obtain hourly scores on the same scale as used in the daily assessment. On these three days the time spent resting was asked for every hour and recorded as the number of minutes spent resting during the last hour.

Actometer

Physical activity was also assessed using the actometer, an accelerometer worn around the ankle for two weeks. The actometer consists of a piezo electric sensor that is sensitive in three directions. Accelerations of the sensor larger than a predefined threshold are considered as activity and are stored into an internal memory. Each second the micro controller reads and resets the counter of the actometer. The integration counter is set at five minutes providing every five minutes an activity score that is stored into the internal memory of the actometer. At the end of the registration period data are fed into an external computer. The actometer has been used in several previous studies on CFS and is a good measure of actual physical activity[13,22].

Daily assessment

Based on the mean of the recorded number of movements every five minutes during a day, for each day an average daily actometer score was computed. As for the self-observation data, on the day of the MET only the data obtained after the maximal exercise test took place were used to compute the mean of that day.

Hourly assessment

For the day before, the day of and the day after the MET mean scores per hour were computed as the mean of the recorded number of movements of every five minutes during the past hour.

Procedure

Daily procedure

All patients and controls were given the self-observation list and the actometer to keep for three days before up to five days after the MET. Daily scores of the three days before the MET were used to compute a baseline score. Daily scores obtained at the day of the MET and at the five days after the MET were compared with baseline to detect the impact of the MET on symptoms and activity on a daily level (see statistical analyses).

Hourly procedure

Within each couple a CFS patient and his control performed the MET at the same day of the week and within all but three of the couples the MET was also performed at the same time of the day, with a time difference of less than one hour. Within three couples the time difference of performing the MET was respectively one, two and three hours. Because between couples the time the MET was performed ranged from 9 AM to 4 PM, complete hourly data are only available from 1 hour before up to 6 hours after the MET. Hourly data were collected the day of, the day before and the day after the MET. To detect the impact of the MET on self observed and actometer scores at an hourly level, hourly data obtained at the day of the MET were compared with the hourly data for the same relative time points on the day before and the day after the MET (see statistical analyses).

Statistical analyses

Data analyses were performed using SPSS (version 8.0).

Analyses of baseline data

To control for day to day fluctuations, baseline scores were computed as the average score of the three days before the MET. To test whether these baseline scores were stable, they were analysed by 2 (group) by 3 (day) general linear model repeated measures analyses of variance (GLM RMANOVA).

Analyses of daily data

To analyse the impact of the MET on self observed and actometer scores over days, a 2 (group) by 7 (day) GLM RMANOVA was used, in which the day of and the days after the MET were compared with baseline. Simple contrasts with baseline data were tested for each group separately.

Analyses of hourly data

As within day fluctuations in self observed and actometer scores were to be expected[23,24], diurnal patterns of the day before, the day of and the day after the MET were compared using 2 (group) by 3 (day) by 7 (hour) GLM RM ANOVA. Additionally, as a secondary analysis, a 2 (group) by 3 (day) GLM RM ANOVA was performed for each hour separately. Within groups simple contrasts of one day before the MET compared with respectively the day of the MET and one day after the MET, were tested for each hour separately.

Because we were interested in whether changes in self observed and actometer scores after exercise would differ between CFS patients and their controls, only interaction effects with group are reported. For the same reason simple contrasts with baseline data were tested for each group separately. For exploratory reasons, statistically significant results of these tests of contrasts are shown whether or not a statistically significant interaction effect could be obtained.

For all analyses the significance level was set at 0.05. Effect sizes (η^2) are shown. Due to failing actometers sample sizes concerning actometer data are 16 for CFS and 17 for controls. For all other variables there are 20 subjects in each group.

Results

Patient and control characteristics

Demographic data, CIS-fatigue and SIP scores are shown in table 1. Differences in CIS-fatigue, SIP-8, and duration of complaints were as expected.

Table 1

CHARACTERISTICS OF CFS PATIENTS AND CONTROLS (% OR MEAN (SD); MEDIAN (25TH AND 75TH PERCENTILE) FOR SIP-8)

	CFS (N=20)	Controls (N=20)
Female (%)	60	60
Age (yrs)	34.1 (8.3)	32.8 (7.2)
Fatigue (CIS; range 8-56)	51.7 (5.1)	13.4 (5.1)
Functional impairment (SIP-8)	1743 (1249-2058)	0 (0-0)
Duration of complaints (yrs)	3.2 (2.5)	-

Impact of the MET on fatigue, muscle pain, rest and activity

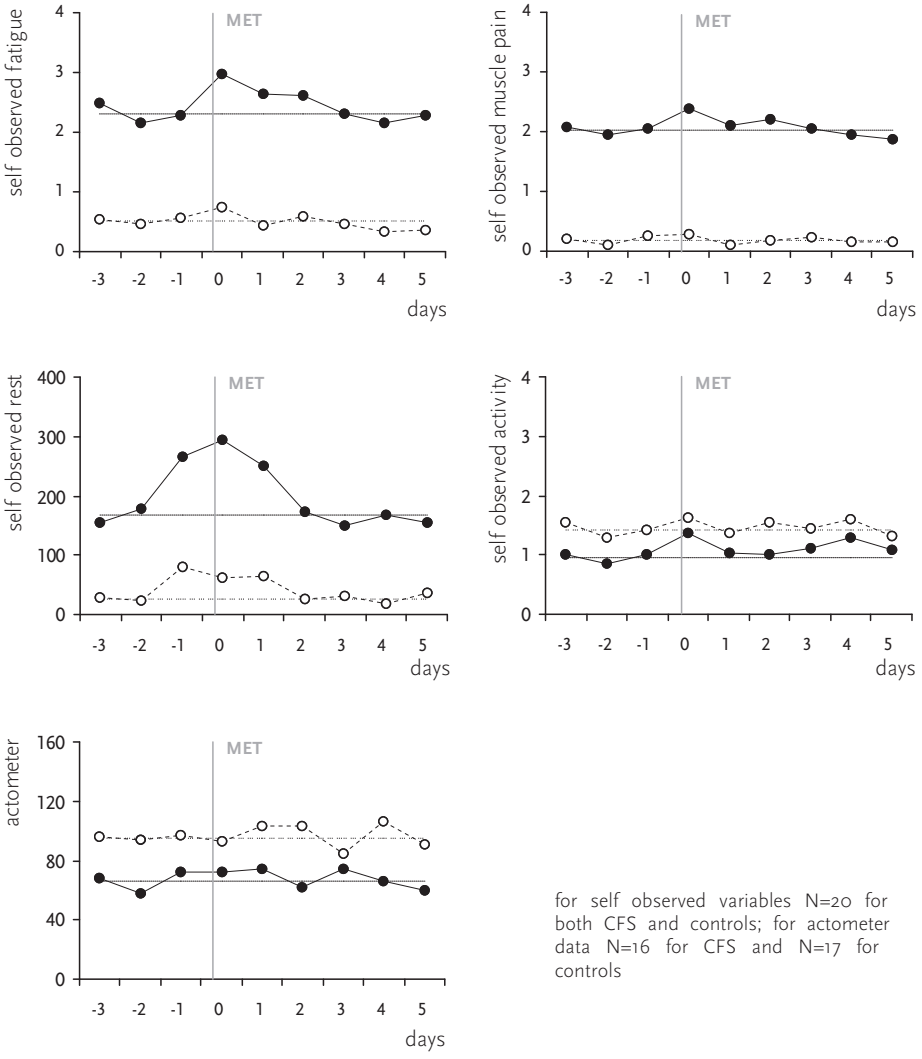
Figure 1 shows the means of all daily observed variables and the actometer from three days before up to five days after the MET for CFS and controls.

Baseline of the daily scores

For daily observed fatigue, daily observed muscle pain, daily observed activity and the actometer the baseline scores of the three days before the MET did not reveal any systematic interaction or within-subjects differences. For these variables means of these three days were used as a baseline. Analyses of the daily observed rest scores of the three days before the MET did show a significant within-subjects difference ($F[2,37]=11.31$, $\eta^2=0.38$, $p<0.001$). No statistically significant group by day interaction effect was found. For daily observed rest, scores of one day before the MET seemed to deviate from the scores at the other two time points in both groups. No average differences were found between the means of daily observed rest three and two days before the MET. Therefore, for both groups the mean of these days were used as a baseline for daily observed rest.

Figure 1

MEAN DAILY SELF OBSERVED AND ACTOMETER SCORES FROM THREE DAYS BEFORE (-3) UP TO FIVE DAYS AFTER (5) THE MET FOR CFS (——; ●) AND CONTROLS (– – –; ○); BASELINE IS REPRESENTED AS A HORIZONTAL LINE (AVERAGE OF THE THREE DAYS BEFORE THE MET; FOR DAILY OBSERVED REST THE AVERAGE OF THE THIRD AND SECOND DAY BEFORE THE MET; CFS —— AND CONTROLS – – –)



for self observed variables N=20 for both CFS and controls; for actometer data N=16 for CFS and N=17 for controls

The daily scores of the days after the MET compared with baseline

For daily observed fatigue a statistically significant day by group effect was found ($F[6,33]=3.74$, $\eta^2=0.38$, $p=0.011$). The contrast procedure revealed that for CFS the day of, one day after and two days after the MET, daily observed fatigue was significantly increased compared with baseline (see table 2). For controls, none of the simple contrasts with baseline were statistically significant. A significant time by group effect was also found for daily observed rest ($F[6,33]=2.66$, $\eta^2=0.33$, $p=0.033$). For CFS the contrast procedure showed a significant increase for daily observed rest between baseline and the day of the MET as well as between baseline and one day after the MET (see table 2). In the control group daily observed rest differed only significantly between one day after the MET and baseline. On daily observed muscle pain, daily observed activity, and the actometer the average profiles of scores after the MET appeared not significantly different for the two groups.

Differences in hourly fatigue, muscle pain, rest and activity scores the day before, the day of and the day after the maximal exercise test.

Mean hourly self observed scores of fatigue, muscle pain, rest and activity the day before, the day of and the day after the MET are illustrated in figure 2. No statistically significant group by day by hour effects were found, neither for any of the hourly self observed nor for the hourly actometer scores. Group by day GLM RM ANOVA's on the hourly scores for each hour separately as well as the accompanying contrast procedures are shown in table 3 and table 4a and 4b respectively.

Table 2

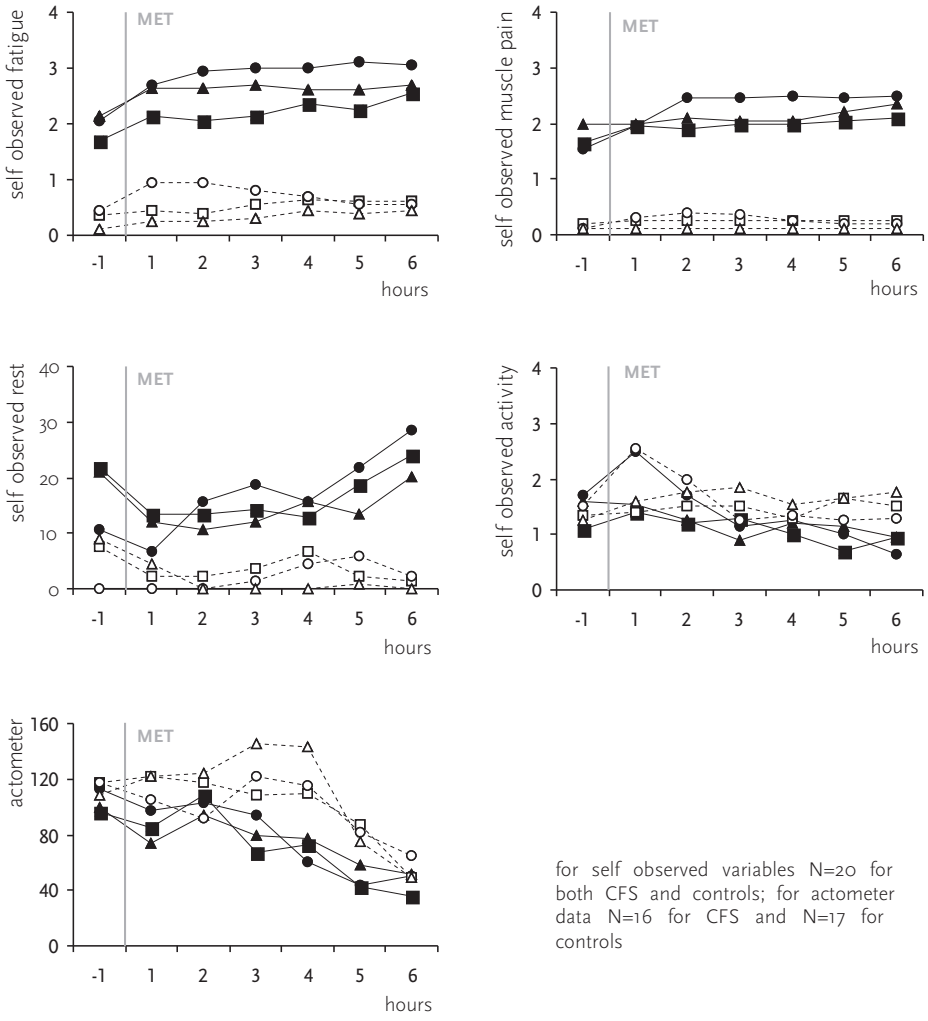
SIMPLE CONTRASTS COMPARING DAILY SCORES THE DAY OF (0) UP TO FIVE DAYS AFTER (5) THE MET WITH BASELINE (BL) FOR CFS AND CONTROLS

		contrast with baseline[1]					
	day-BL	CFS			Controls		
		F	η^2	p-value	F	η^2	p-value
Self observed fatigue	**0-BL**	27.99	0.42	<0.001			NS
	1-BL	10.98	0.22	0.002			NS
	2-BL	6.88	0.15	0.012			NS
	3-BL			NS			NS
	4-BL			NS			NS
	5-BL			NS			NS
Self observed muscle pain	**0-BL**	6.99	0.16	0.012			NS
	1-BL			NS			NS
	2-BL			NS			NS
	3-BL			NS			NS
	4-BL			NS			NS
	5-BL			NS			NS
Self observed rest	**0-BL**	39.65	0.51	<0.001			NS
	1-BL	25.62	0.40	<0.001	5.68	0.13	0.022
	2-BL			NS			NS
	3-BL			NS			NS
	4-BL			NS			NS
	5-BL			NS			NS
Self observed activity	**0-BL**	7.27	0.16	0.010			NS
	1-BL			NS			NS
	2-BL			NS			NS
	3-BL			NS			NS
	4-BL	4.77	0.11	0.035			NS
	5-BL			NS			NS
Actometer	**0-BL**			NS			NS
	1-BL			NS			NS
	2-BL			NS			NS
	3-BL			NS			NS
	4-BL			NS			NS
	5-BL			NS			NS

[1] df [1,38]; for actometer df [1,31]

Figure 2

MEAN HOURLY SELF OBSERVED AND ACTOMETER SCORES FOR CFS (—— ; CLOSED SYMBOLS) AND CONTROLS (- - - ; OPEN SYMBOLS) 1 HOUR BEFORE (-1) UP TO 6 HOURS AFTER (6) THE MET, THE DAY OF THE MET (● ○), COMPARED WITH THE HOURLY DATA OF THE RELATED POINTS OF TIME OF THE DAY BEFORE (■ □) AND THE DAY AFTER (▲ △) THE MET



for self observed variables N=20 for both CFS and controls; for actometer data N=16 for CFS and N=17 for controls

Table 3

DAY-BY-GROUP INTERACTION EFFECTS FOR SELF OBSERVED AND ACTOMETER SCORES PER HOUR RELATIVE TO THE TIME OF THE DAY THE MET WAS TAKEN (DAYS COMPARED ARE THE DAY BEFORE, THE DAY OF, AND THE DAY AFTER THE MET

		GLM RM ANOVA[1]		
	hour	day x group		
		F	η^2	p-value
Self observed fatigue	-1	4.80	0.21	0.014
	1	4.39	0.19	0.020
	2	4.54	0.20	0.017
	3	5.74	0.24	0.007
	4			NS
	5	5.24	0.22	0.010
	6			NS
Self observed muscle pain	-1			NS
	1			NS
	2			NS
	3			NS
	4			NS
	5			NS
	6			NS
Self observed rest	-1			NS
	1			NS
	2			NS
	3			NS
	4			NS
	5			NS
	6			NS
Self observed activity	-1			NS
	1			NS
	2			NS
	3	3.41	0.16	0.044
	4			NS
	5			NS
	6			NS
Actometer	-1			NS
	1			NS
	2			NS
	3			NS
	4			NS
	5			NS
	6			NS

[1] df [2,37]; for actometer df [2,30]

Table 4a

SIMPLE CONTRASTS OF HOURLY SELF OBSERVED AND ACTOMETER SCORES COMPARING THE DAY OF THE MET WITH THE DAY BEFORE (THE HOURS ARE RELATIVE TO THE TIME OF THE DAY THE MET WAS TAKEN), SEPARATELY FOR CFS AND CONTROLS

	hour	contrast between the day of and the day before the MET[1]					
		CFS			Controls		
		F	η^2	p-value	F	η^2	p-value
Self observed fatigue	-1			NS			NS
	1	5.48	0.13	0.025	4.53	0.11	0.040
	2	13.17	0.26	0.001	4.92	0.11	0.033
	3	14.34	0.27	<0.001			NS
	4	11.68	0.24	0.002			NS
	5	18.61	0.33	<0.001			NS
	6	8.66	0.19	0.006			NS
Self observed muscle pain	-1			NS			NS
	1			NS			NS
	2			NS			NS
	3			NS			NS
	4	6.13	0.14	0.018			NS
	5	6.16	0.14	0.018			NS
	6	8.84	0.19	0.005			NS
Self observed rest	-1	4.51	0.11	0.040			NS
	1	6.04	0.14	0.019			NS
	2			NS			NS
	3			NS			NS
	4			NS			NS
	5			NS			NS
	6			NS			NS
Self observed activity	-1	5.78	0.13	0.021			NS
	1	8.33	0.18	0.006	9.11	0.19	0.005
	2			NS			NS
	3			NS			NS
	4			NS			NS
	5			NS			NS
	6			NS			NS
Actometer	-1			NS			NS
	1			NS			NS
	2			NS			NS
	3			NS			NS
	4			NS			NS
	5			NS			NS
	6			NS			NS

[1] df [1,38]; for actometer df [1,31]

Table 4b

SIMPLE CONTRASTS OF HOURLY SELF OBSERVED AND ACTOMETER SCORES COMPARING THE DAY AFTER THE MET WITH THE DAY BEFORE (THE HOURS ARE RELATIVE TO THE TIME OF THE DAY THE MET WAS TAKEN), SEPARATELY FOR CFS AND CONTROLS

	hour	contrast between the day after and the day before the MET[1]					
		CFS			Controls		
		F	η^2	p-value	F	η^2	p-value
Self observed fatigue	-1	6.23	0.14	0.017			NS
	1	8.56	0.18	0.006			NS
	2	11.72	0.24	0.001			NS
	3	11.11	0.23	0.002			NS
	4			NS			NS
	5			NS			NS
	6			NS			NS
Self observed muscle pain	-1			NS			NS
	1			NS			NS
	2			NS			NS
	3			NS			NS
	4			NS			NS
	5			NS			NS
	6			NS			NS
Self observed rest	-1			NS			NS
	1			NS			NS
	2			NS			NS
	3			NS			NS
	4			NS			NS
	5			NS			NS
	6			NS			NS
Self observed activity	-1	4.66	0.11	0.037			NS
	1			NS			NS
	2			NS			NS
	3			NS			NS
	4			NS			NS
	5	4.97	0.12	0.032			NS
	6			NS			NS
Actometer	-1			NS			NS
	1			NS			NS
	2			NS			NS
	3			NS			NS
	4			NS	4.19	0.12	0.049
	5			NS			NS
	6	6.75	0.18	0.014			NS

[1] df [1,38]; for actometer df [1,31]

Discussion

In CFS fatigue after exercise increased more and was of longer duration as compared with healthy controls. Whereas for controls fatigue returned to baseline after two hours, for CFS a significant increase of daily observed fatigue was found up to two days after the exercise test. Muscle pain was increased only in CFS and only on the day of the exercise test, specifically four to six hours after the MET. This increase in CFS, however, is not significantly different from the increase of muscle pain in controls.

A striking result is that, for CFS as well as for controls, minutes spent resting increased the day before the exercise test. Both groups seem to anticipate the exercise test. Although both groups also reported more time spent resting the day after the MET, the reported minutes rest on the day of the exercise test increased more for CFS than for controls. For both groups the daily observed minutes spent resting returned to normal not earlier than on the second day after the exercise test. Due to an increase of daily observed rest on the day before, the day of, and the day after the MET for both groups, diurnal patterns did not show many differences. CFS patients only seemed to spend fewer minutes resting during the hour before as well as the hour after the MET, compared with the related hourly scores of the day before. Probably this is a consequence of travelling to the hospital for the exercise test.

Contrary to what was expected, the actometer did not reveal a decrease of physical activity after the exercise test. The self observed daily level of activity increased in CFS the day of the MET, when compared with baseline. Furthermore, both CFS patients and controls considered themselves to have been more active during the hour after the exercise test, whereas CFS patients also showed a somewhat increased daily observed level of activity the hour before the exercise. Probably, again these reported increases of activity surrounding the exercise test are a consequence of the subjects travel to the hospital. The few other statistically significant findings concerning activity are hard to explain. Whereas these late effects were not hypothesized and are not congruent, they probably have to be considered random fluctuations. So, although there are some findings that activity increases after exercise, no decrease of activity after exercise was found.

One might argue that the maximal exercise test was not strenuous enough to find an effect on activity. This is however unlikely. Data concerning physiological aspects of the MET showed that both CFS patients and controls reached a highly increased level of perceived exertion at maximal workload[16]. As we have shown now, CFS patients were even more fatigued several days thereafter, while their level of physical activity remains unchanged.

Another hypothesis is that, although the fitness of the CFS patients in this study is not different from controls[16], fitness influences the extent of exacerbation of symptoms and decrease of activity after exercise. It can be hypothesized that CFS patients with a lower physical fitness perceive a greater increase of fatigue after exercise than CFS patients having a better physical fitness. Finally it might be that the maximum workload reached during the exercise test influences the effect of the MET on symptoms and activity. However, studying these hypotheses would need much larger sample sizes.

Confidence intervals for the actometer were broad for both groups (data not shown). Therefore changes are not easily significant and interpreting actometer scores is difficult. Possibly, heterogeneity of the CFS group might hide effects for subgroups of patients. It has been found that, based on their level of physical activity as assessed with the actometer, different groups of CFS patients can be distinguished[22]. Some CFS patients appeared to be really inactive, called passive CFS patients, whereas others are still rather active, called pervasively active CFS patients. In between, most CFS patients have a fluctuating activity pattern, called moderately active. One might hypothesize that the impact on symptoms and activity of an exercise test might be more present in passive CFS patients. In the present study sample sizes are too small to test this hypothesis. Only three CFS patients in our study were passive patients. This percentage of passive CFS patients in our sample is congruent with the number of passive CFS patients in other samples[22].

Although actometer results seem rather congruent with daily observed activity scores, there is a striking discrepancy between the actometer results and self-observed minutes spent resting. Post-hoc analyses do not show any significant correlations between the actometer and daily observed rest or daily observed activity. This agrees with findings of Vercoulen and colleagues[13] who found that daily observed activity is a subjective rating of activity, whereas the actometer is a behavioural measure. The same might account for daily observed rest. It might be that CFS patients as well as controls perceive themselves to rest more, but actually don't. An alternative explanation is that subjects do not so much diminish physical activities but withdraw from other, e.g. mental and social, activities.

In our study weekday patterns are not taken into account. In a similar study De Vries and colleagues[25] showed that for symptomatic Cambodia veterans as well as for healthy Cambodia veterans, activity levels on Saturday and Sundays were lower in comparison with weekdays. The couples in our study did not all perform the MET on the same weekday, nor did all couples perform the MET at exactly the same time of the day. However, within each couple the exercise test was performed on the same day and mostly at the same time, thus controlling for weekday and time of the day effects.

One might speculate about the influence of CFS patients selecting their own controls. We used neighbourhood controls, matched by age and sex, and – more or less by nature – for social background. Although we have not characterized these controls with regard to sedentary behaviour, it is likely that the social selection controls for that.

Finally, due to a small sample size, our analyses may not have had enough power to detect all relevant effects. Especially for the actometer data, in which data for four CFS patients and three controls were missing. To prevent the sample sizes to become smaller, the accompanying subject in the other group was not deleted. So, actometer data were not completely matched anymore. Our use of contrast tests, however, increased power somewhat. The significant effects found were moderate to large in terms of proportion of variance explained (η^2). Another methodological difficulty is the use of the data of the day of the MET. The scores on the variables for this day were based solely on measurements taken after the MET was performed. This was done because our focus was on the effect of the MET. One could argue that within-day fluctuations might cause a difference between days only based on the fact that scores in the afternoon might differ from scores of a complete day. Because the findings of the analyses over days are congruent with findings over hours, this is not very likely.

So, the perception of CFS patients that they remain more fatigued for days after strenuous exercise is in accordance with the findings in this study. However, their level of physical activity does not change. Still, both CFS patients and controls report more minutes spent resting the day before, the day of and the day after exercise.

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Cognitive behaviour group therapy for chronic fatigue syndrome: a non-randomised wait list controlled study

6

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Abstract

Background. It has been demonstrated that individual cognitive behaviour therapy is an effective treatment for chronic fatigue syndrome (CFS). Aim of the present study was to investigate the effectiveness of cognitive behaviour group therapy (CBGT) in an unselected group of CFS patients. Additionally, pre-treatment characteristics of CFS patients who improve after CBGT were explored.

Methods. In a non-randomised wait list controlled design 31 patients were allocated to CBGT, and 36 to the wait list condition. CBGT consisted of 12 two-hour sessions during six months. Main outcome measures were fatigue (CIS-fatigue) and functional impairment (SIP-8).

Results. A moderate effect on fatigue in favour of CBGT was found. For functional impairment the effect was opposite to what was expected. Patients improved after CBGT had less complaints at baseline compared to non-improved patients.

Conclusions. An explanation for the moderate effect might be that during CBGT rest and relaxation were too much emphasised. Furthermore, an unselected group of CFS patients and therapists inexperienced with CB(G)T for CFS participated. Suggestions to improve CBGT for future research are given.

Introduction

Chronic fatigue syndrome (CFS) is characterised by severe fatigue lasting for at least six months, for which no somatic explanation can be found, and which leads to severe disability in daily life[1]. Although the cause of CFS is still unknown, several perpetuating factors have been identified. A model of perpetuating factors in CFS showed that a strong focus on bodily symptoms, low levels of physical activity and a poor sense of control contribute to an increase in the severity of fatigue and functional impairment[2]. Strong somatic attributions lead to lower levels of physical activity. Several protocols for cognitive behaviour therapy (CBT) for CFS have been developed[3-6]. In several studies individual CBT for CFS has proven to be effective, even at follow up[7-12]. Three recent reviews conclude that CBT and graded exercise are the only interventions in CFS with proven effectiveness[13-15]. Further research on CBT for patients with milder forms of CFS or for CFS inpatients as well as research on the effectiveness of cognitive behaviour group therapy (CBGT) was recommended[13].

Some first reports on the feasibility and effectiveness of forms of CBT for CFS other than ambulatory individual therapy show positive results. These uncontrolled studies concern CBT in an inpatient setting, CBT as a part of a multidisciplinary intervention, CBT in a general hospital setting and CBT for adolescents with CFS[16-20]. There is no literature on the effect of CBGT for CFS. Only one study evaluated the effect of focused group therapy for CFS, in a controlled design[21]. This non-CBT group intervention had no effect on fatigue and impairment. In another study it was shown that support groups for CFS patients had no effect on fatigue and impairment either[9].

Aim of the present controlled study was to investigate the effectiveness of CBGT for CFS. Additionally pre-treatment characteristics of CFS patients who improve after CBGT were explored.

Method

Design

CBGT was compared with a wait list condition. CBGT, lasting six months, was offered in two centres, the Department of Psychotherapy of the Maastricht Mental Health Institute and the Department of Medical Psychology of the University Medical Centre Nijmegen. For ethical reasons patients in the wait list condition were offered CBGT after the wait period of six months. Only data of the controlled part of the study were used to test the effectiveness of CBGT.

Participants

CFS patients were diagnosed and referred by the outpatient clinic of the departments of General Internal Medicine of the University Medical Centre of Nijmegen or Maastricht. All patients fulfilled the Fukuda criteria for CFS or idiopathic chronic fatigue[1]. Consecutive patients with the diagnosis CFS or idiopathic chronic fatigue were asked to participate in the current study. Patients were included if they had a CIS-fatigue score of 35 or more and a SIP-8 score of 700 or more (see baseline measures). Furthermore, they had to be willing to stop other treatments for CFS during CBGT. Pivotal to CBT for CFS is that the patient becomes aware that the progress made can be attributed to the changes in his or her cognitions and behaviours. When the patient is undergoing two treatments simultaneously it is difficult to say which of the two interventions accounts for the improvements. To prevent withdrawal after inclusion, we added this prerequisite for CBGT before inclusion. If both of the inclusion criteria were fulfilled, informed consent was obtained. Patients were allocated to CBGT until the first group was full. The next groups consisted partly of patients from the wait list condition and partly of recently referred patients. Baseline assessment took place in the two weeks prior to the start of CBGT, for the wait list condition six months prior to the start of the next CBGT. Ultimately, eight groups of seven to ten patients were completed.

Cognitive Behaviour Group Therapy

In CBGT cognitions and behaviour known to perpetuate fatigue in CFS were the focus of change[2]. Cognitions concerning a negative self-efficacy and somatic attributions were challenged. Further, CFS patients were taught to behave according to their own limits and to have adequate periods of rest and relaxation. Thereafter, a graded activity program took place. Homework assignments and a course book were used. CBGT consisted of 12 two-hour sessions during six months. CBGT was presented as a course in 'coping with fatigue'.

There were two therapists for each group. Six therapists in four different couples participated. All therapists were inexperienced with group therapy and inexperienced with CBT for CFS. They were weekly supervised by a therapist experienced in working with groups and CBT for CFS.

Wait list condition

Patients in the wait list condition had no restrictions. They were free to undertake everything they would usually do.

Measurements

Primary outcome measures

The subscale fatigue of the Checklist Individual Strength (CIS-fatigue) was used to measure fatigue[22]. This subscale has eight items scored on a 7-point Likert scale (range 8-56). High scores reflect high levels of fatigue.

Eight subscales of the Sickness Impact Profile (SIP-8) were used to measure functional impairment[22-23]. The eight subscales used were home management, mobility, alertness behaviour, sleep/rest, ambulation, social interactions, work, and recreation and pastimes. A total score was calculated by addition of the weights of items (range 0-5799). High scores reflect high levels of functional impairment. Comparison data were available[22].

Secondary outcome measures

Fatigue was also assessed using a 12-day self-observation list[24]. Scores were obtained four times a day (9 a.m., noon, 6 p.m., 10 p.m.) on a scale from 0 (not fatigued) to 4 (very severe fatigued). Daily-observed fatigue is represented as the mean of the total daily-observed fatigue scores over 12 days. So the range for daily-observed fatigue is 0 to 16. In the same way as for fatigue daily-observed pain was measured.

In a general questionnaire an item concerning the hours that the patient had been working in a job the last week was added.

Psychological distress was measured with the Symptom Checklist 90 (SCL-90)[25]. This scale consists of 90 items scored on a 5-point Likert scale (range 90-450). High scores reflect high psychological distress. Depression was measured with the Beck Depression Inventory (BDI)[26]. High scores reflect high levels of depression (range 0-63).

Self-rated improvement was only asked for after CBGT. Answers were given on a 4 point scale: 'completely recovered', 'better or much better', 'the same', or 'worse' [27-28]. This variable is dichotomised in 'better or recovered' and 'the same or worse'.

Perpetuating factors

Physical attributions were measured with four items concerning the conviction that CFS is a consequence of 'something physical', 'a virus', 'the immune system', or 'some physical disease' [28].

Items are answered on a Likert scale from 1 (not convinced at all) to 4 (completely convinced). Scores range from 4 (no physical attributions) to 16 (strong physical attributions).
Self-efficacy was measured with five items concerning whether the patient thinks he can influence his complaints[9,28]. Four questions were answered on a 5-point Likert scale, 1 question on a 4-point Likert scale. Scores range from 5 (low self-efficacy) to 24 (high self-efficacy).

Avoidance of activity was measured with five items scored on a 4-point Likert scale[22]. Questions were asked with respect to avoidance of physical activity as a way of coping with complaints. Scores range from 5 (no avoidance of activity) to 20 (strong avoidance of activity).
Focusing on bodily symptoms was measured by the subscale somatisation of the SCL-90[25,27]. The subscale consists of 12 items scored on a 5-point Likert scale. Scores ranges from 0 to 60.

Statistical analyses

Two (group) by two (time) interaction effects of repeated measures analyses of variance (RM ANOVA's) were used to analyse treatment effect.
Patients were divided in improved or non-improved after CBGT according to self-rated improvement. Predictors of treatment outcome were explored comparing baseline characteristics of these improved and non-improved CFS patients. Because of small sample sizes, pre-treatment differences were analysed with the Mann-Whitney U test for continuous variables. For discrete variables Pearson Chi-Squares were used.
The significance level was set at 0.05. Effects with a p-value between 0.05 and 0.10 were accepted as a trend. All analyses were performed using SPSS version 10.0.

Results

Patient flow is displayed in figure 1. Of the total 67 eligible patients, 31 CFS patients were allocated to CBGT and 36 CFS patients were allocated to the wait list condition. Two patients dropped out during treatment. No post-test data are available from these patients. So, 29 CFS patients in the CBGT condition and 36 CFS patients in the wait list control condition entered into post-test.

Figure 1

PATIENT FLOW

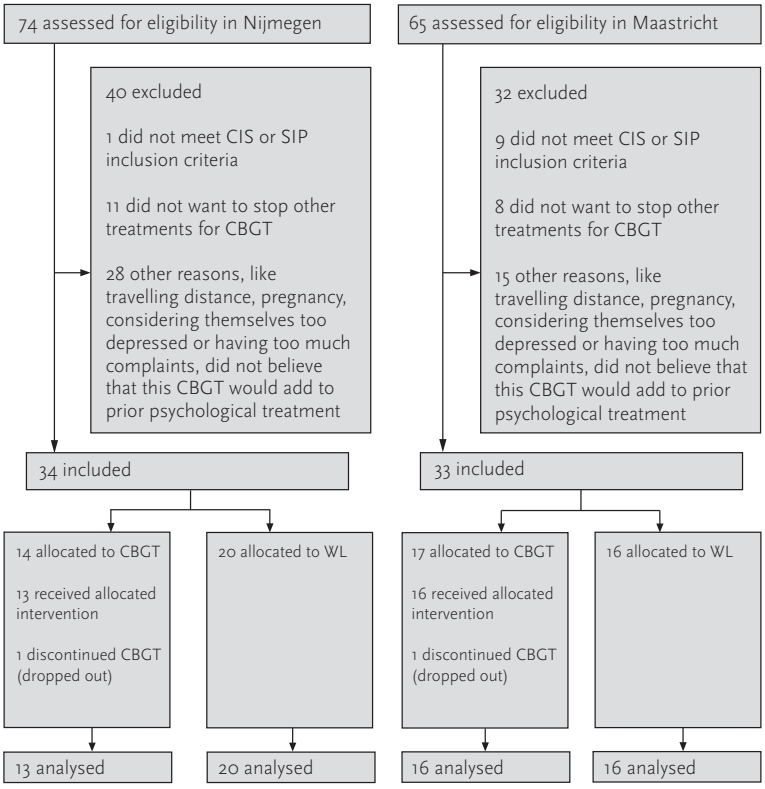

Table 1

DEMOGRAPHIC CHARACTERISTICS OF PATIENTS IN THE CBGT AND THE WAIT LIST CONDITION (WL); VALUES DISPLAYED ARE MEANS (SD) OR PERCENTAGE (N)

	CBGT (N=31)	WL (N=36)
Age (yrs)	37.4 (8.6)	35.8 (9.0)
Educational attainment (1=low, 7=high)	4.3 (1.7)	4.7 (1.6)
Female (%)	67.7 (21)	77.8 (28)

Patient characteristics at baseline

Demographic data are displayed in table 1. No apparent differences between CBGT and the wait list condition emerged. Two patients' only fulfilled Fukuda criteria for idiopathic fatigue, the others fulfilled Fukuda criteria for CFS. Mean duration of complaints was 6.2 years (sd 5.2) and 5.3 years (sd 4.5) in the CBGT and wait list condition respectively. All baseline data (table 2) were as expected for CFS[22, 27, 28].

CBGT compared to the wait list control group

Interaction effects of the RM ANOVA's are displayed in table 2.

Primary outcome measures

On CIS-fatigue an interaction effect with a p-value of 0.099 was found, in favour of CBGT. Functional impairment showed a significant interaction effect (p=0.004) in favour of the wait list condition. Functional impairment did not change after CBGT, but declined in the wait list condition

Secondary outcome measures

For daily observed fatigue, daily-observed pain, hours working, psychological well-being and depression, no significant interaction effects were found.

Self-rated improvement scores were available of 27 of 29 patients after CBGT. Ten (37%) of these CFS patients rated themselves improved.

Perpetuating factors

Concerning perpetuating factors, a significant interaction effect was found for physical attributions (p=0.023) and avoidance of activity (p=0.001). Physical attributions decreased after CBGT and increased in the wait list condition. Avoidance of activity increased after CBGT and decreased in the wait list condition. On self-efficacy and focusing on bodily symptoms no interaction effects were found.

Pre-treatment differences of CFS patients improved and non-improved after CBGT

Comparing the CFS patients who rated themselves improved after CBGT with those who did not, it was found that improved patients reported significantly less functional impairment, less

Table 2

INTERACTION EFFECTS OF RM ANOVA'S BETWEEN BASELINE AND 6 MONTHS, CBGT COMPARED TO THE WAIT LIST CONDITION (WL)

	CBGT		WL		interaction effect	
	Mean (sd)	**95% CI**	**Mean (sd)**	**95% CI**	**F-value [df]**	**p-value**
Primary outcome measures						
Fatigue (CIS-fatigue)						
baseline	51.0 (5.0)	49.0-53.1	50.8 (5.6)	49.0-52.6		
6 months	45.6 (9.6)	42.6-48.7	48.4 (6.2)	45.7-51.1	2.807 [1,61]	0.099
Functional impairment (SIP-8)						
baseline	1707 (713)	1474-1940	1710 (528)	1502-1919		
6 months	1736 (714)	1516-1955	1417 (444)	1221-1613	9.117 [1,61]	0.004
Secondary outcome measures						
Daily-observed fatigue						
baseline	8.6 (2.7)	7.6-9.6	9.4 (2.4)	8.6-10.3		
6 months	8.2 (3.4)	6.9-9.4	9.0 (3.0)	7.9-10.1	0.005 [1,58]	0.943
Daily-observed pain						
baseline	6.0 (3.8)	4.7-7.4	6.9 (3.2)	5.7-8.1		
6 months	6.2 (4.3)	4.7-7.8	6.7 (3.7)	5.3-8.1	0.460 [1,57]	0.500
Hours working (mean/week)						
baseline	5.5 (9.9)	1.8-9.2	5.6 (9.6)	2.3-9.0		
6 months	6.4 (11.7)	2.3-10.6	6.7 (10.5)	2.9-10.5	0.003 [1,60]	0.958
Psychological distress (SCL-90)						
baseline	165.4 (39.1)	150.6-180.2	162.7 (37.8)	149.3-176.0		
6 months	162.1 (48.0)	145.6-178.6	154.2 (38.1)	139.3-169.1	0.580 [1,58]	0.449
Depression (BDI)						
baseline	15.2 (8.3)	12.5-17.8	13.7 (6.0)	11.2-16.1		
6 months	11.9 (6.8)	9.7-14.2	11.4 (5.3)	9.3-13.5	0.643 [1.63]	0.426
Perpetuating factors						
Physical attributions						
baseline	11.2 (2.0)	10.4-11.9	11.8 (1.8)	11.1-12.6		
6 months	10.6 (2.4)	9.7-11.4	12.2 (1.9)	11.4-13.0	5.502 [1,51]	0.023
Self-efficacy						
baseline	15.9 (3.2)	14.5-17.3	14.9 (3.8)	13.7-16.1		
6 months	18.5 (3.3)	17.1-19.8	16.9 (3.6)	15.7-18.1	0.453 [1,58]	0.504
Avoidance of activity						
baseline	7.6 (2.6)	6.4-8.7	8.0 (3.3)	6.9-9.1		
6 months	9.1 (2.4)	8.2-10.0	7.4 (2.2)	6.6-8.3	12.743 [1,54]	0.001
Focusing on bodily symptoms						
baseline	28.8 (8.2)	25.9-31.8	31.5 (7.1)	28.9-34.2		
6 months	27.9 (9.0)	24.7-31.1	29.2 (7.6)	26.3-32.1	0.714 [1,58]	0.402

daily observed fatigue, and less daily observed pain at baseline (table 3). For the pre-treatment variable 'mean hours working a week' a trend was found with improved patients working more hours at baseline compared to non-improved patients.

Table 3

PRE-TREATMENT DIFFERENCES OF CFS PATIENTS IMPROVED AND NON-IMPROVED AFTER CBGT FOR DISCRETE VARIABLES (% PRESENTED) AND CONTINUOUS VARIABLES (MEAN (SD) PRESENTED) RESPECTIVELY.

	Better or much better (N=10)	Same or worse (N=17)	Chi-Square	p-value [a]
CBGT in Nijmegen	50	41	0.199	NS
Being female	80	65	0.706	NS

	Better or much better (N=10)-	Same or worse (N=17)	MWU	Z	p-value [a]
Age	38.0 (7.2)	36.2 (8.9)	76.0	-0.453	NS
Educational attainment	4.7 (1.6)	4.2 (1.7)	70.5	-0.741	NS
Duration of complaints	4.9 (4.5)	6.8 (5.6)	66.0	-0.961	NS
Fatigue (CIS-fatigue)	50.7 (4.2)	52.1 (4.2)	63.0	-1.113	NS
Functional impairment (SIP-8)	1330 (417)	1985 (730)	42.0	-2.159	0.031
Daily-observed fatigue	7.4 (2.6)	9.7 (2.3)	34.0	-2.277	0.023
Daily-observed pain	4.5 (2.6)	7.8 (3.5)	35.0	-2.220	0.026
Hours working (mean/week)	10.9 (12.8)	2.6 (6.6)	55.0	-1.867	0.062
Psychological distress (SCL-90)	151.8 (51.1)	168.8 (36.1)	60.5	-1.231	NS
Depression (BDI)	12.1 (6.7)	17.4 (9.0)	53.5	-1.590	NS
Physical attributions	10.9 (1.8)	11.5 (2.2)	64.5	-0.656	NS
Self-efficacy	16.7 (3.3)	15.4 (3.2)	57.5	-1.195	NS
Avoidance of activity	7.6 (2.8)	7.0 (2.5)	68.5	-0.835	NS
Focusing on bodily symptoms	10.9 (1.8)	11.5 (2.2)	68.0	-0.855	NS

[a] p-values <0.10 are displayed

Discussion

A trend was found that CBGT has a positive effect on fatigue in CFS. The changes in functional impairment were opposite to what was expected. On secondary outcome measures no significant improvement was found. After CBGT 37% considered themselves improved. Although it was not the focus of this study, post hoc analyses showed no significant differences in the effectiveness of CBGT between the two participating centres.

Treatment effect in our study is low compared to most studies on individual CBT for CFS[7-10]. Whereas in these studies self-rated improvement ranged from 57% up to 70%, ours was 37%. In the control conditions of these other studies, self-rated improvement ranged from 23% up to 31%. Unfortunately, in our study self-rated improvement was not assessed after the wait list period.

Contrary to our findings, most studies on individual CBT for CFS find an effect on functional impairment in favour of the treatment condition. In the study of Prins and colleagues[9], functional impairment also declined in the support groups as well as in the natural course condition, but after CBT functional impairment declined more. It seems that in our CBGT improvement on functional impairment was interfered. This might be related to the finding that avoidance of activity increased after CBGT, and not after the wait list period. Asking the therapists afterwards, it seems that during CBGT there has been spent too much time on rest and relaxation, whereas starting the graded activity program was postponed for too long. It seemed to have been too difficult to get a group of patients starting and sustain the activity program. Furthermore, CBGT was presented as a course in 'coping with fatigue'. Once avoidance of activity had led to less fatigue, patients may have been satisfied yet. On this point, patients may have reinforced each other's maladaptive behaviours.

One might dispute the effectiveness and suitability of CBGT for CFS. The main advantage of group therapy lies in the fact that several patients can be treated simultaneously. Modelling processes by seeing other members of the group might facilitate behaviour change. However, group therapy for CFS also has disadvantages. In group therapy CFS patients may reinforce dysfunctional behaviour and resistance against psychological treatment. Furthermore, in group therapy it is much harder to individualise CBT treatment to individual needs.

Yet, based on our current study and some recent studies on individual CBT for CFS, recommendations to improve the effectiveness and suitability of CBGT for CFS can be made. In trials on individual CBT for CFS it was found that engagement in a claim for a disability related benefit

during CBT predicted less improvement after individual CBT for CFS[12,29]. Our CBGT started before completion of these studies. In the present study it was found that CFS patients with less severe complaints did profit most of CBGT. In future research on the effectiveness of CBGT for CFS these findings will have to be taken into account.

Another explanation for the moderate effect of CBGT might be that the therapists had no prior experience with CB(G)T for CFS. Only Prins and colleagues[9] performed a multi-centre trial using therapists inexperienced with CBT for CFS as well. In that study 83% of the therapists stated that they agreed that 'CFS patients are more difficult to treat than patients with psychological complaints', and 64% agreed that 'CFS patients are more difficult to treat than other patients with somatic complaints'[30]. For our study this might count even more, since the therapists were inexperienced both in group therapy and in CBT for CFS.

Finally, based on this and former studies the treatment protocol CB(G)T for CFS has been improved. Rest and relaxation are less emphasised, and for passive CFS patients the treatment protocol has been adapted[9]. Recently, lack of social support has been identified as an important determinant of CFS and a new perpetuating factor[31,32]. Dealing with a lack of social support may also have to become a more prominent aspect of CBT for CFS.

For future research on CBGT in CFS it is recommended to select CFS patients not engaged in a claim for a disability related benefit during CBT and with less severe complaints. Furthermore, therapists should be experienced in group therapy as well as CBT for CFS.

In the current study we found a moderate effect of CBGT on fatigue, in an unselected group of CFS patients, and with newly trained therapists. Future research is necessary to further investigate the suitability of CBGT for (subgroups of) CFS patients.

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Cognitive behaviour therapy for chronic fatigue syndrome: a multicentre randomised controlled trial

7

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Abstract

Background. Cognitive behaviour therapy (CBT) seems a promising treatment for chronic fatigue syndrome (CFS), but the applicability of this treatment outside specialised settings has been questioned. We compared CBT with guided support groups and the natural course in a randomised trial at three centres.

Methods. Of 476 patients diagnosed with CFS, 278 were eligible and willing to take part. 93 were randomly assigned CBT (administered by 13 therapists recently trained in this technique for CFS), 94 were assigned the support-group approach, and 91 the control natural course. Multidimensional assessments were done at baseline, 8 months, and 14 months. The primary outcome variables were fatigue severity (on the checklist individual strength) and functional impairment (on the sickness impact profile) at 8 and 14 months. Data were analysed by intention to treat.

Findings. 241 patients had complete data (83 CBT, 80 support groups, 78 natural course) at 8 months. At 14 months CBT was significantly more effective than both control conditions for fatigue severity (CBT vs support groups 5.8 [2.2-9.4]; CBT vs natural course 5.6 [2.1-9.0]) and for functional impairment (CBT vs support groups 263 [38-488]; CBT vs natural course 222 [3-441]. Support groups were not more effective for CFS patients than the natural course. Among the CBT group, clinically significant improvement was seen in fatigue severity for 20 of 58 (35%), in Karnofsky performance status for 28 of 57 (49%), and self-rated improvement for 29 of 58 (50%). Prognostic factors for outcome after CBT were higher sense of control predicting more improvement, and a passive activity pattern and focusing on bodily symptoms predicting less improvement.

Interpretation. CBT was more effective than guided support groups and the natural course in a multicentre trial with many therapists. Our study showed a lower proportion of patients with improvement than CBT trials with a few highly skilled therapists.

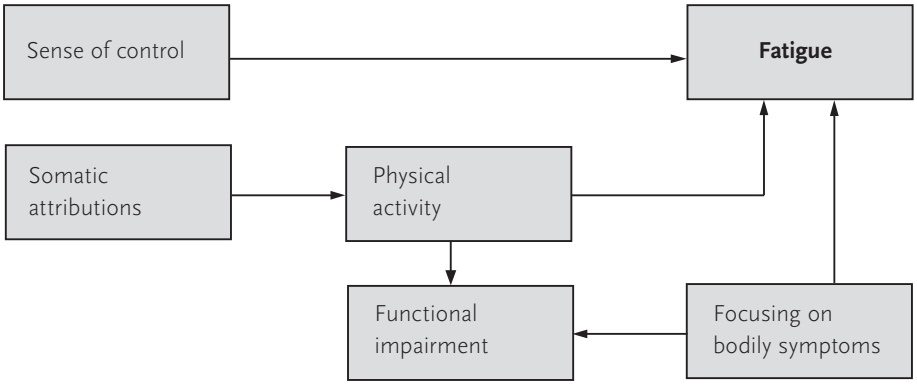
Introduction

Chronic fatigue syndrome (CFS) is characterised by persistent or relapsing unexplained fatigue, of new or definite onset and lasting for at least six months. Fatigue is not the result of an organic disease or ongoing exertion, rest does not alleviate it, and there is substantial limitation of occupational, educational, social and personal activities[1]. No cause of CFS has been found, and most patients do not recover. No somatic or pharmacological treatments have proven to be effective[2]. Cognitive behaviour therapy (CBT) seems to be a promising treatment of CFS[3-5]. Two randomised controlled trials reported positive results[6,7]. A recent review questioned whether these results can be generalised outside specialist centres were only a few highly skilled therapists, or even a single therapist administered CBT. Furthermore, in both studies the primary outcome variable was functional impairment and not fatigue, the main complaint of CFS patients.
In our study, criticisms of both previous randomised trials were addressed. The effectiveness of CBT was tested in a multicentre randomised trial. CBT was compared with a treatment condition, guided support groups, and a control condition, the natural course. CBT was administered in three different centres rather than one specialist centre. Experts taught the treatment protocol to many therapists with no previous experience in CBT for CFS. Guided support groups should control for the absence of specific cognitive-behavioural interventions and the presence of therapist attention and treatment expectations. We assumed that support groups, as in other chronic diseases[8,9], might contribute to a feeling of mutual understanding, acceptance and support and thereby have a healing effect.

In this study, the outcome variables were fatigue severity and functional impairment, with the same instruments for inclusion and outcome. Moreover, CBT for CFS was based on a statistically tested model of perpetuating factors in CFS[10,11] rather than on hypothesised factors in CFS or on treatments of other medically unexplained syndromes. The model of CFS is shown in figure 1. Focusing on bodily symptoms, low levels of physical activity and sense of control contribute to increasing severity of fatigue and functional impairment. CBT is directed at these perpetuating factors. The main aim of our multicenter trial was to show the effectiveness of CBT for patients with CFS. Our hypothesis that fatigue severity and functional impairment should decrease significantly more in the group of patients assigned CBT than in patients in the control groups.

Figure 1

MODEL OF CFS DEVELOPED AND TESTED WITH LISREL (A PROGRAM FOR THE ESTIMATION OF LINEAR STRUCTURAL RELATIONS) [10]



Patients and methods

Patients

All patients with a major complaint of fatigue referred to the outpatient clinic of the departments of internal medicine of the University Medical Centre Nijmegen and the University Hospital Maastricht between October, 1996, and January, 1998, were assessed by means of detailed history, physical examination, and computer assessment of questionnaires. Patients were eligible for the study if they met the US Centers for Disease Control and Prevention criteria for CFS[1], with the exception of the criterion requiring four of eight additional symptoms to be present. Severe fatigue and severe functional impairment were defined by cut-off scores: a score of 40 or more on the subscale fatigue severity of the Checklist Individual Strength and a score of 800 or more on the Sickness Impact Profile. Additional inclusion criteria for this study were age between 18 and 60 years, and residence within 1.5 hour travelling time of one of the study centres. Additional exclusion criteria were previous or current participation in CFS research, pregnancy, and current treatment to achieve pregnancy.

A sample size of 80 patients per group was estimated assuming significance of 5%, power of 90%, a dropout rate of 20%, and a medium effect size on the actometer, the measure of our multidimensional approach in need of most individuals to show improvement. Multidimensional assessment has been recommended for studies assessing the effect of therapeutic interventions for CFS, to measure change in different dimensions of the patients' functioning[12]. During the trial the dropout rate was higher than that estimated in the calculation of sample size. Therefore, the target sample size for inclusion was set at 90 patients per study group.

Design and procedures

The study was an open multicentre randomised controlled trial in which individual CBT was compared to participation in guided support groups and with the natural course, a control condition in which no treatment was offered. The ethics committees of the three participating centres gave approval for the study. Treatment effects were expected in the primary outcome variables fatigue severity and functional impairment and were explored in the secondary outcome variables: Karnofsky performance status, psychological well-being, quality of life, and work. The predictive role of perpetuating factors in the model of CFS was tested exploratively also.

Patients who met the trial criteria and were willing to take part in the trial had to give informed written consent. To ensure adequate generation and adequate concealment in the allocation process[13], patients were allocated sequentially to one of three conditions, by blockwise random-

isation (block size six), separately for each centre. The allocation was concealed in series of envelopes for each centre and assigned by (assistant) researchers before baseline in the presence of the patient, in order of enrolment in the trial.

CBT and support groups took place in three different settings, the Department of Medical Psychology of the University Medical Centre Nijmegen, the Department of Psychiatry of the Leiden University Medical Centre, and the Department of Psychotherapy of the Maastricht Mental Health Institute. CBT and support groups were administered by different therapists and on different days to prevent contamination.

CBT consisted of 16 sessions of one hour over 8 months. Patients in this group had to meet the requirements of no further medical examinations or other treatments for CFS during the trial. These conditions were essential in reducing focusing on bodily symptoms and somatic attributions. A preliminary version of CBT has been extensively described. An essential part of CBT is self-control: this means that the CFS patient is acquiring control over symptoms instead of dependence on physicians prescribing treatments or medications. In this study, CBT was outlined in a treatment protocol. First, the model of perpetuating factors was explained, and the therapist attempted to motivate the patient for CBT. Next, fatigue-related cognitions were challenged to diminish somatic attributions, to improve sense of control over symptoms, and to facilitate behaviour change. Patients were encouraged to attain and maintain a base level of physical activity needed to prevent bursts of activity and resultant extreme fatigue. Subsequently, a structured activity programme was started. After a gradual increase of physical activity, a plan for work rehabilitation was outlined and carried out. For patients without a job, rehabilitation in other personal activities was achieved. The final sessions dealt with relapse prevention and further improvement of self-control.

Thirteen behaviour therapists of three different disciplines (psychologist, psychiatrists, and health scientists) took part. Therapists varied in previous CBT (non-CFS-related) experience, because the study was done with the therapists available within the three centres. However, none of the therapists was familiar with CBT for CFS at the start of the trial. Two experts in CBT for CFS (GB, EB) trained the therapists in using the treatment protocol in a workshop, consisting of two blocks of two days each, separated by a month, in which the therapists started the treatment of two CFS patients in a pilot study. Therapists were supervised once every two weeks throughout the trial. Patients were allocated to therapists in a fixed sequence by the researcher in order of patients' random allocation to CBT in each centre separately. An integrity check of a random sample of 5% of all audiotaped CBT sessions was done. An independent judge used a checklist to rate the degree and the amount of time spent on the basic elements of CBT (restructuring of fatigue-related cognitions, attaining a base level of daily activity, gradual increase of physical activity, and returning to work or personal activities) in each session. The analyses showed that 91.5% of the time spent in therapy was relevant for CBT and that 87% of the sessions were adequate or good overall.

The guided support groups were similar to CBT in terms of time spent and treatment schedule.

Each group, consisting of about eight patients, had 11 meetings of one and an half hour over 8 months. One social worker was available for all 11 groups in the three centres. The treatment orientation was non-directive and client-centred. The social worker was supervised once every two weeks by a psychotherapist, who had no links with CBT or CFS. The goal of the support groups was to offer mutual understanding and recognition by means of exchanging experiences with one central theme during each meeting. In this study group, patients were free to have other examinations or treatments. All support-group sessions were videotaped, and the tapes were randomly checked to make sure that the social worker was not using CBT-like strategies. In the control condition natural course, no interventions were offered, and no further requirements were made. Patients were free to have other examinations or treatments.

Assessment

Multidimensional assessments were made at baseline, at 8 months, and a follow-up (14 months). The baseline assessment included the screening assessment before randomisation (fatigue, functional impairment, criteria of the Centers for Disease Control and Prevention) and those made immediately after randomisation.

Fatigue severity was assessed by a subscale of the checklist individual strength[14]. In this questionnaire, the patient is asked about fatigue in the two weeks preceding the assessment. The subscale consists of eight items, each scored on a 7-point Likert scale (range 8-56). The questionnaire has good reliability (Cronbach's alpha varying from 0.83 to 0.92) and discriminative validity[12,14,15].

Functional impairment was measured by the sickness impact profile[16,17]. This widely used measure has good reliability and content validity[18]. As in our previous studies, a total score was calculated by addition of the weights of items (range 0-5799) in eight subscales: home management, mobility, alertness behaviour, sleep/rest, ambulation, social interactions, work, and recreation and pastimes. Comparison data for CFS patients were available[12].

The Karnofsky performance status scale is a descriptive, ordinal scale. An independent clinical psychologist rated the patient's functional status in 10-point intervals from 0 to 100. The validity and reliability of this scale have been shown in several populations[19,20]. Comparison data for CFS patients were available[6].

The symptom checklist 90[21] measured psychological well-being. The scale consists of 90 items scored on a 5-point Likert scale. The total score ranges from 90 to 450. A low total score reflects high psychological well-being. This scale is widely used and the reliability and discriminating validity are good.

The visual analogue scale of the EuroQol[22] measured quality of life. The scale ranges from 0 (worst health status) to 100 (best health status). The EuroQol has been validated in normal populations, patients and in CFS patients[23].

Hours working in a job were recorded on a 24 hour timetable of the 12-day self-observation list[24].

Self-rated improvement was measured at 8 months and at follow-up by one specific question: patients indicated whether they had completely recovered, felt much better, had the same com-

plaints or had become worse compared with the previous measurement. This measure has been validated in several of patients populations and was used in this study as one of the measures for clinically significant improvement[24-26].

The self-efficacy scale, consisting of five questions, measured sense of control in relation to CFS complaints. Four items were scored on a 5-point Likert scale and one item on a 4-point Likert scale. The total score ranges from 5 to 24, a higher score reflecting more sense of control. Cronbach's alpha reliability coefficients range from 0.70 to 0.77[10,12,25].

Somatic attributions with respect to CFS were measured by the causal attribution list consisting of five questions scored on a 4-point Likert scale. The total score ranges from 5 to 20, a higher score indicating stronger somatic attributions. Cronbach's alpha reliability coefficients range from 0.71 in previous studies[12,25] to 0.74 in this study.

Physical activity was measured by the actometer, a motion-sensing device attached to the ankle and worn continuously for 12 days. Such devices are reliable and valid measures of physical activity[27]. The activity pattern of each patient was typified by comparison of daily activity scores with the reference score of CFS patients. Three categories were defined: pervasively passive (90% or more beneath the reference score); moderately active; pervasively active (90% or more above the reference score)[28].

Focusing on bodily symptoms was measured by the subscale somatisation of the symptom checklist 90[21], as in previous studies in which CFS patients were compared with healthy individuals and patients with multiple sclerosis[10,29]. The subscale consists of 12 items scored on a 5-point Likert scale. The score ranges from 0 to 60.

Analysis

A general linear model for repeated measurements (by the method of mixed linear models) was used to analyse the effects of CBT on the two primary variables (fatigue severity and functional impairment) and the secondary variables Karnofsky performance status, symptom checklist 90, Euroqol, and hours working in a job. Differences at 8 months and 14 months from baseline were used as repeated measurements, with treatment (three levels), centre (three), time (two levels) and their first-order interactions as fixed factors. The covariance matrix was specified as unstructured (implying a general structure), estimation method used was restricted maximum likelihood, and Satterthwaite's method was used to estimate denominator degrees of freedom. First, we tested, for the primary variables, whether the centre terms could be regarded as redundant (likelihood ratio test comparing the two models). If this was the case for both variables, reduced models with treatment and time factors and their interaction were used in all subsequent analyses. All treatment effects, as well as differences between treatments were estimated within these models; 95% CI were computed from these estimates and their standard errors. We used the procedure MIXED from the SAS package (version 6.12). Although the methods of analysis for the primary and secondary variables are the same, results for the latter should be regarded as exploratory.

To define clinically significant improvement in fatigue severity, we first calculated for each patient a reliable change index to decide whether statistically significant improvement had occurred (reliable change >1.64, $p<0.05$). Second, a cut-off score of 36 or lower was calculated to decide whether a patient's score had moved from the range of CFS patients to the range of healthy individuals[30]. A patient was classified as showing clinically significant improvement if both criteria were met.

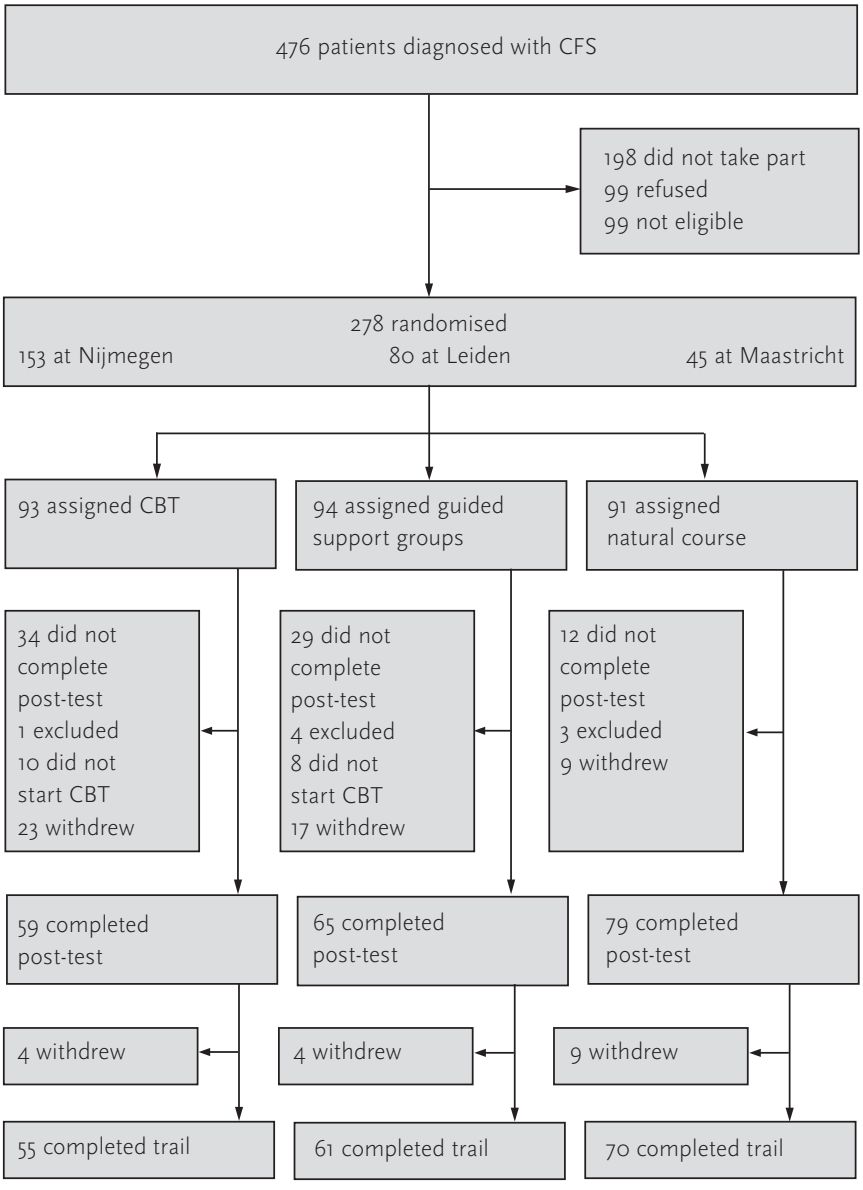
Improvement in the Karnofsky performance status was explored also, so that we could compare the results with those of Sharpe and colleaques[6]. Clinically significant improvement was defined as an improvement of 10 points or more and a score of 80 or more.

Self-rated improvement was defined as a patient's indication that he or she was completely recovered or felt much better. The categorical variables which were calculated by the procedures applied on the original variables checklist individual strength, Karnofsky performance status and self-rated improvement, were compared between treatments by Fisher's exact test at 8 months and 14 months.

Analyses of possible predictors were done with multiple linear regressions. The predictors were included and excluded with the stepwise method. Independent variables were treatment, baseline value of the dependent variable, age, sex, duration of complaints, education, and the baseline values of the perpetuating factors: sense of control, activity pattern, focusing on bodily symptoms, and somatic attributions, and all first-order interactions between treatment and other factors. The main interest was the relation between predictors and the direct treatment effect. Therefore, only the outcomes at 8 months were analysed. Results from these analyses should be regarded as exploratory.

Figure 2

TRIAL PROFILE



Results

518 patients were referred to the University Medical Centre Nijmegen with a major complaint of fatigue; CFS was diagnosed in 410. Another 66 patients were diagnosed with CFS at the University Hospital Maastricht. Of these 476 patients, 99 did not meet the eligibility criteria and 99 refused to take part. The remaining 278 patients were randomly assigned to the study groups at the centres of Nijmegen, Leiden and Maastricht (figure 2). In total, 93 patients entered the CBT group, 94 the support groups, and 91 the control natural course group. Six patients were excluded: five developed other diseases during the trial and one was pregnant at baseline. After randomisation, two patients were found not to meet the criteria for CFS because they had premorbid anorexia nervosa. Thus, the trial consisted of 270 patients (92 CBT, 90 support groups, 88 control groups), of whom 203 (75%) completed 8 months and 186 (69%) 14 months in the trial. 18 patients did not start treatment. 49 withdrew during the test phase and 17 withdrew during follow-up. Withdrawal was defined differently for the three groups. In the natural course group, only patients not attending the assessments were classified as withdrawing, whereas in the two intervention groups those who stopped treatment were also counted. Moreover, in contrast to CBT, frequent non-attendance in the guided support groups had no consequences for further treatment, unless a patient declared the intention to withdraw. This difference was reflected in the significant difference in mean hours of attending treatment between CBT group and the guided support group (15.6 vs 13.2; $p<0.001$). Table 1 shows the baseline characteristics of the three groups.

At 8 months, 241 patients (89%) had complete data (83 CBT, 80 support groups, 78 natural course). At 14 months, 196 patients (73%) had complete data (58 CBT, 62 support groups, 76 natural course). The data of these patients were included in the analyses. Only 9% of the patients had missing data at one or both post-treatment assessments.

For both primary outcome variables, a reduced model without any centre term could be used ($p=0.437$ for checklist individual strength, fatigue; $p=0.202$ for sickness impact profile, likelihood ratio test with 8 df). Consequently, all subsequent analyses were done with such models.

In the primary outcome variables, significant differences between the treatment effects of CBT support groups, and natural course were found (figure 3). Estimated differences are shown in table 2.

Table 1

BASELINE CHARACTERISTICS OF STUDY PARTICIPANTS

	CBT (N= 92)	Guided support groups (N= 90)	Natural course (N= 88)
Demography			
Age in years	36.2 (9.4)	37.1 (10.6)	36.7 (10.3)
Educational attainment	3.9 (1.6)	4.3 (1.4)	4.4 (1.6)
(1=low to 7=high)			
M/F *	22/70	19/71	17/71
CFS features			
Duration in years	4.9 (4.8)	6.6 (6.4)	5.3 (5.4)
CIS fatigue	52.2 (3.9)	52.3 (4.0)	51.9 (4.1)
SIP total	1755 (613)	1842 (560)	1859 (671)
Karnofsky	71.5 (8.5)	71.2 (7.5)	70.8 (7.9)
SCL-90	170 (38.5)	169 (41.5)	166 (36.0)
EuroQol	46 (17)	43 (16)	40 (14)
Work, hours in 12 days	16.3 (21.1)	12.8 (19.1)	13.5 (18.6)
Sense of control	14.8 (3.5)	14.6 (3.1)	14.6 (3.6)
Somatic attributions	13.9 (2.8)	14.1 (2.5)	13.5 (2.4)
Focusing on bodily symptoms	30.7 (6.9)	30.0 (7.6)	29.8 (7.2)
Activity pattern#			
Generally passive*	21 (23%)	16 (19%)	24 (29%)
Moderately active*	56 (62%)	53 (62%)	50 (59%)
Generally active*	13 (15%)	16 (19%)	10 (12%)

CIS = checklist individual strength; SIP = sickness impact profile; SCL-90 = symptom checklist 90.
Data are mean (sd) or *numbers of participants. # 11 cases had incomplete actometer data and are not included

Figure 3

EFFECT OF THREE STUDY CONDITIONS ON THE TWO PRIMARY OUTCOME VARIABLES, FATIGUE SEVERITY (CIS) AND FUNCTIONAL IMPAIRMENT (SIP)

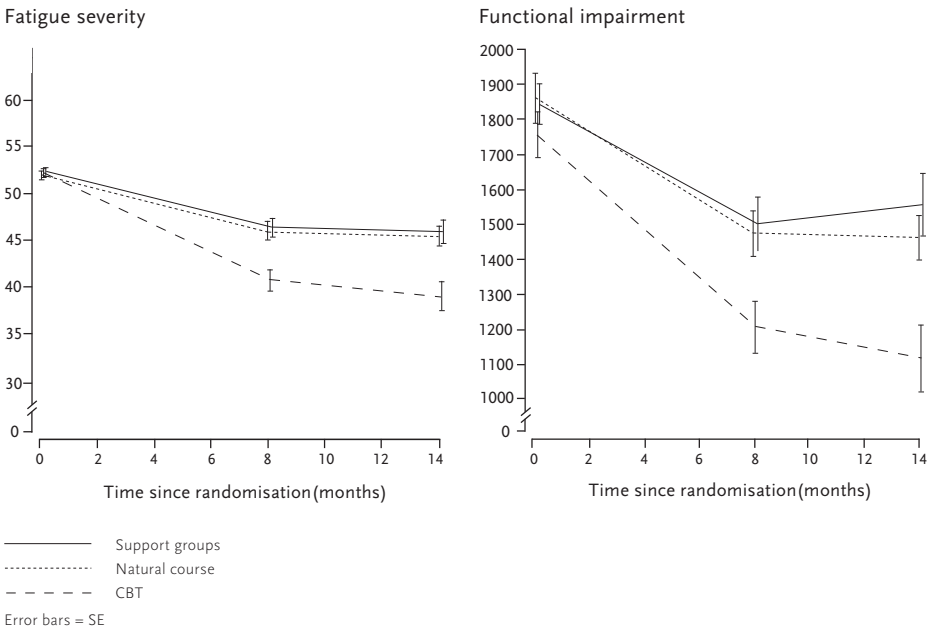


Table 2

ESTIMATED EFFECT OF CBT COMPARED WITH SUPPORT GROUPS AND NATURAL COURSE ON FATIGUE SEVERITY (CIS) AND FUNCTIONAL IMPAIRMENT (SIP)

	CBT vs support groups		CBT vs natural course	
	Treatment effect (95%CI)	**p-value**	**Treatment effect (95%CI)**	**p-value**
CIS 8 months	6.0 (3.1-9.0)	0.0001	6.0 (3.1-9.0)	0.0001
14 months	5.8 (2.2-9.4)	0.0015	5.6 (2.1-9.0)	0.0016
SIP 8 months	217 (26-408)	0.0261	213 (22-403)	0.0287
14 months	263 (38-488)	0.0223	222 (3-441)	0.0470

Table 3

ESTIMATED EFFECT OF CBT COMPARED WITH SUPPORT GROUPS AND NATURAL COURSE ON SECONDARY ENDPOINTS

		CBT vs support groups		CBT vs natural course	
		Treatment effect (95% CI)	**p-value**	**Treatment effect (95% CI)**	**p-value**
Karnofsky	8 months	-5.7 (-8.4 to -3.1)	0.0001	-5.2 (-7.8 to -2.6)	0.0001
	14 months	-6.3 (-9.6 to -3.0)	0.0002	-5.4 (-8.6 to -2.2)	0.0009
SCL-90	8 months	13.9 (4.3 to 23.5)	0.0048	13.4 (4.0 to 22.7)	0.0053
	14 months	11.2 (1.1 to 21.3)	0.0304	6.7 (-3.0 to 16.5)	0.1767
EuroQol	8 months	-7.8 (-14.0 to -1.8)	0.0114	-4.0 (-10.0 to 2.0)	0.1878
	14 months	-9.2 (-15.6 to - 2.8)	0.0049	-2.3 (-8.4 to 3.8)	0.4619
Work	8 months	-5.6 (-11.7 to 0.4)	0.0681	-2.9 (-8.8 to 3.0)	0.3362
	14 months	-9.6 (-17.1 to - 2.0)	0.0132	-5.9 (-13.2 to 1.4)	0.1134

Table 3 gives the estimated differences between the study groups in secondary outcome variables. At 8 months, improvement in Karnofsky performance status, psychological well-being and quality of life was statistically significantly greater in the CBT group than in either of the other groups. Differences in the time spent working in a job did not reach the 5% level of significance. Statistically significant treatment effects between CBT and support groups were found in all secondary outcome variables at 14 months. Treatment effects of CBT and natural course showed statistically significant differences for the Karnofsky performance status at both 8 and 14 months and for psychological well-being at 8 months.

Table 4 shows the proportions of patients with clinically significant improvements in fatigue severity, Karnofsky performance status, and self-rated improvement. For these three variables, the proportion with clinically significant improvement was statistically significantly higher in CBT than in the control conditions.

All factors in the stepwise regression related to the outcome measures fatigue severity and functional impairment at $p<0.05$ are presented in order of entrance in the model in table 5. The improvement in fatigue severity at 8 months was predicted by interactions of CBT with sense of control and by a passive activity pattern, rather than by CBT alone. In the CBT study groups, patients with a greater sense of control at baseline had a larger decrease in fatigue severity at 8 months, immediately after CBT, than patients with lower sense of control. The reverse was true for patients with a passive activity pattern; they improved less than patients with other activity patterns.

Improvement in functional impairment at 8 months was predicted by CBT alone and by interaction of CBT and focusing on bodily symptoms. Patients assigned CBT improved more than patients in both control groups. However, patients in CBT with a high level of focusing on bodily symptoms were improved less than patients with lower scores on this factor

Table 4

CLINICALLY SIGNIFICANT IMPROVEMENT IN THE TREATMENT GROUPS FOR FATIGUE SEVERITY (CIS), KARNOFSKY PERFORMANCE STATUS, AND SELF-RATED IMPROVEMENT

		Number of patients with improvement/total			p-value*	
		CBT	Support groups (SG)	Natural course (NC)	CBT vs SG	CBT vs NC
8 months	**CIS fatigue**	27/83 (33%)	10/80 (13%)	10/78 (13%)	0.003	0.005
	Karnofsky	29/71 (41%)	11/69 (16%)	9/75 (12%)	0.001	<0.001
	Self-rated improvement	42/74 (57%)	12/71 (17%)	23/78 (30%)	<0.001	0.001
14 months	**CIS fatigue**	20/58 (35%)	8/62 (13%)	13/76 (17%)	0.009	0.026
	Karnofsky	28/57 (49%)	12/62 (19%)	17/75 (23%)	0.001	0.001
	Self-rated improvement	29/58 (50%)	9/62 (15%)	24/76 (32%)	<0.001	0.034

* Fisher's exact test

Table 5

PARAMETER ESTIMATES, SE AND PARTIAL R^2 OF ALL FACTORS RELATED TO THE OUTCOME MEASURE FATIGUE SEVERITY OR FUNCTIONAL IMPAIRMENT (BASELINE MINUS 8 MONTHS) AT $p<0.05$ IN ORDER OF ENTRANCE TO THE MODELS

Factor	Coefficient (SE)	Partial R^2
Fatigue severity (CIS)		
CBT x sense of control	0.5088 (0.0883)	0.0856
Baseline CIS	0.7010 (0.1469)	0.0515
Focusing on bodily symptoms	-0.2611 (0.0838)	0.0368
CBT x passive activity pattern	-8.902 (2.545)	0.0208
Moderately activity pattern	-3.439 (1.229)	0.0229
Sense of control	0.3535 (0.1723)	0.0147
Sex (female)	2.761 (1.386)	0.0133
Functional impairment (SIP)		
Baseline SIP	0.4767 (0.0604)	0.1788
CBT	1005 (281.9)	0.0321
CBT x focusing on bodily symptoms	-25.06 (8.838)	0.0266

CIS=checklist individual strength; SIP=sickness impact profile

Discussion

In this study, CBT was more effective for CFS patients than guided support groups or the natural course. Intention-to-treat analyses showed clinically significant improvement in fatigue severity, Karnofsky performance status, and self-rated improvement in substantial proportions of patients treated with CBT. An unexpected finding was that support groups were no more effective than the natural course (figure 3). This finding contrasts with other chronic diseases in which support groups are beneficial. However, 80% or more of the patients experienced mutual understanding in the support group, and rated the contact with the therapist and the atmosphere in the group as good. These findings suggest that clinical improvement and patients' satisfaction are not correlated and may be independent.

There was a large withdrawal rate in the trial, especially in the CBT and support groups. Many CFS patients eagerly expect a medical solution for their complaints and are quite sceptical about psychological treatments. Others expected more benefit from medical examinations or alternative treatments. These patients may have withdrawn prematurely. The physical burden of travelling to the centre for therapy was another reason for patients to withdraw. However, many patients who withdrew during treatment were willing to attend for assessment of the primary outcome variables. At 8 months, there was a withdrawal rate of 25%, but only 11% of the patients had missing data. Results of the analyses depend among other assumptions on that of 'missingness at random' which means that missingness is possibly related to the observed data, but, conditional on these data, not to the (unknown) value of the variable itself. Although we cannot prove the assumption, we can partially check it as follows[31]: comparison of characteristics of completers and non-completers (age, sex, duration of complaints, centre, and all baseline measures) showed no differences. Furthermore, the results of the intention-to-treat analyses and those of the analyses of the completers, were mostly qualitatively similar.

Supporting evidence of the effectiveness of CBT was found in the significant improvement in Karnofsky performance status rated by an independent clinical psychologist in the group of patients treated with CBT compared with the control groups. A significant treatment effect on quality of life, psychological well-being, and work rehabilitation was only found in the comparisons of CBT with support groups and not between CBT and natural course. We were especially interested in work rehabilitation, a new element in the tested treatment protocol. The final goal of CBT for CFS included work rehabilitation for patients who used to be active in a job and resumption of other personal activities for patients without a job. We could not conclude the extent to which this goal was reached, because only hours working in a job were measured.

However, in our sample of 270 patients only 33% had a job at baseline, whereas 76% had been employed before the onset of CFS. For the unemployed patients, securing employment within the limited period of treatment and follow-up would be difficult, although most of these patients did resume personal activities. The development of adequate measures of rehabilitation should have high priority in future research on CBT for CFS.

The proportions of patients with clinically significant improvement in this study were lower than in other CBT trials. We suggest several explanations for this discrepancy. First, therapists in this study had no clinical experience with CFS patients at the start of the trial. Afterwards, 82% of the therapists agreed with the statement that CFS patients are more difficult to treat than patients with psychiatric diagnoses, and 54% agreed that CFS patients are more difficult to treat than patients with other functional somatic syndromes. Second, criteria for statistical and clinical significance in this study were more stringent than in the previous trials. The cut-off score for clinically significant improvement was based on normative comparisons of CFS patients and healthy individuals and was perhaps overly stringent. In a recent evaluation of the concept of clinically significant improvement[32], Kendall and colleagues questioned whether patients should be compared with a non-representative 'supernormal' sample of healthy people, from which all individuals with any psychological or physical disorders are excluded. Third, the treatment protocol seemed not to be suitable for a group of CFS patients who showed passive activity patterns. Analyses of prognostic factors showed that patients with this activity pattern and patients with a strong tendency to focus on bodily symptoms improved less than did patients not characterised by one of these factors. In our clinical practice, the treatment protocol has now been adjusted to both aspects. In the new treatment protocol, the emphasis is now on impeding cognitions and behaviour rather than on symptoms. Furthermore, a different treatment protocol has been developed for patients with a passive activity pattern. The early emphasis in CBT on a base level of daily activity, so important for moderately active CFS patients, seems to increase the fear of physical activity in passive CFS patients and impedes the subsequent gradual increase of physical activity. Therefore, CBT for patients with passive activity patterns starts with building up physical activity, whereas more active patients still start with attaining and maintaining a base level of daily activity.

The results of this trial suggest that CBT can be transferred from CFS research clinics to therapists with no previous experience in CBT. This transfer is essential to detach the treatment from medical research settings, in which only a limited number of CFS patients can be treated. To increase accessibility of this treatment for all CFS patients in future, CBT will have to be implemented outside university medical settings. This idea accords with Wessely and colleagues' suggestion of transferring the diagnosis and treatment of functional somatic syndromes from medical subspecialists to more broadly based general physicians aided by psychiatrists or psychologists[33]. Ideally, general practitioners should diagnose CFS and refer patients to psychotherapists for CBT, without detours to medical specialists, as in other functional somatic syndromes[33]. Before this goal can be reached, expertise needs to be generalised from specialist centres to general practitioners and behaviour therapists in general (mental) health settings.

Contributors

Judith Prins co-ordinated data collection and analysis and drafted the report. Gijs Bleijenberg developed the original idea, was responsible for the study design, study co-ordination, training of therapists, and development of treatment protocol, and contributed to writing of the paper. Ellen Bazelmans contributed to study design, training of therapists, and treatment protocol, supervised the therapists, and contributed to editing of the paper. Lammy Elving was responsible for the development of the diagnostic protocol and selection of patients and contributed to data collection and editing of the paper. Theo de Boo was responsible for data analysis and statistics and contributed to the writing of the paper. Johan Severens contributed to study design and editing of the paper. Gert-Jan van der Wilt contributed to the study design and data analysis. Philip Spinhoven contributed to study co-ordination, data collection and editing of the paper. Jos W.M. van der Meer developed the original idea and contributed to study design, study coordination, and writing.

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Manual-based cognitive behaviour therapy for chronic fatigue syndrome: therapists' adherence and perceptions

8

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Abstract

Several randomised controlled trials have indicated that cognitive behaviour therapy is an effective treatment for chronic fatigue syndrome. In one of these studies 13 therapists applied cognitive behaviour therapy for chronic fatigue syndrome in 83 chronic fatigue syndrome patients. In the present study therapists' adherence and perceptions of the manual are studied. Following completion of the study the therapists were asked to complete a questionnaire. Audio taped sessions were conducted to verify the therapists' adherence. Analyses of the audiotapes showed that in 87% of the sessions this appeared to be the case. The questionnaire revealed that the therapists found it more difficult to treat patients with chronic fatigue syndrome than to treat patients with psychological or other physical problems. Treatment aspects posing the most problems were integrating individual problems into the standardized treatment, dealing with the patients' lack of confidence in the treatment and handling insufficient motivation.

Introduction

Several randomised controlled trials have shown that cognitive behaviour therapy is an effective treatment for chronic fatigue syndrome (CFS)[1-4], even at follow-up[5,6]. Reviews showed that graded exercise and cognitive behaviour therapy are the treatments of choice for CFS[7-9]. In our multi-centre randomised controlled trial cognitive behaviour therapy was compared with guided support groups and natural course[3]. The study included 270 CFS patients. Thirteen therapists treated 83 CFS patients with cognitive behaviour therapy. Intention-to-treat analyses showed cognitive behaviour therapy to be more effective than the two other conditions for both of the two main outcome measures, i.e. fatigue severity and functional impairment.

In the present study the transference of the treatment manual is explored. Two questions are relevant in this context. First, to what extent did the therapists, who were extensively trained and supervised, comply with the various aspects of the treatment manual during the actual sessions? Secondly, what is their judgement as to the treatment's suitability for transfer? What are, in their views, the difficult and less difficult aspects of the prescribed treatment, what are the manual's shortcomings, and which of the treatment aspects do they think are suitable to be applied by therapists without additional training?

To find answers to these questions each of the therapists completed a questionnaire, following conclusion of all treatment sessions.

Method

Treatment manual

The treatment manual 'CBT for CFS' was founded on empirical knowledge and experience with CFS patients in clinical practice. The rationale of the intervention was based on the model of perpetuating factors in CFS[10,11]. This model claims that a negative self-efficacy (the idea of having no control over symptoms), strong somatic attributions, a low activity level and a tendency to focus on bodily sensations, negatively affect fatigue severity and functional impairment in CFS patients. When complaints are attributed to a somatic cause (somatic attributions) this will lead to a reduced level of physical activity, which in turn affects the severity of the fatigue. A negative self-efficacy and strong focus on physical sensations will have a direct impact on the severity of the fatigue. Based on this model, the standardized cognitive behaviour therapy for the treatment of CFS was aimed at decreasing somatic attributions, increasing self-efficacy, and restoring the balance in activity patterns. The underlying principle of the treatment was that although we do not know what actually caused the complaints, we do know which factors help maintain the symptoms. The treatment therefore challenged the perpetuating factors. The final treatment goal was the patient's full recovery and a resumption of his or her normal activities.

The manual starts with a general outline of the treatment (table 1). Next, for each session the goal is described, together with the associated target cognitions for the patient, the therapist's aims and objectives, and the session's program. Also, an indication of time, in minutes, to be allotted to each treatment aspect was provided. The manual further contained practical suggestions on how to effectuate the various interventions, sometimes with verbatim descriptions and detailed examples using the same two fictitious patients throughout the manual. The treatment consisted of 16 sessions distributed over a period of eight months. The first sessions were on a weekly basis with the frequency of the subsequent sessions decreasing from once every two weeks to once every three weeks down to once a month. The content of the first eight sessions was fully structured. The subsequent sessions could be tailored more to the individual patient. The manual comprised 79 pages. Preparation and evaluation forms were provided separately. With these forms the therapists were encouraged to reflect, both prior to and following each session, on how to integrate the patient's individual situation with the manual.

Table 1

OUTLINE OF THE TREATMENT MANUAL

Step	Session	Methodology	Homework assignment
1. Referral and intake	1	introduction; discussion of assessment; fine-tuning of expectations; role of spouse; modus operandi	
2. Preparing patient for treatment and explanation of treatment goal	1, 2	discussion of goal; return to work	
3. Explanation of the model	1, 2	views on somatic factors; role of cognitions and behaviours	
4. Exercises to prevent the fatigue from getting worse	1, 2, 3 .... (through - out)	learning to think differently; accepting cognitions; peak-stop exercise	registration of cognitions; peak-stop exercise
5. Learning to recognize and respect limitations, and following this through	2, 3, 4 .... (through - out)	peak-stop exercise; learning to rest; base level; rationale activity program; coping with the environment: learning to say no; lowering demands: changing way of thinking	registration of cognitions; peak-stop exercise; writing down base level
6. Practicing gradual expansion of limits	5, 6, 7 .... (through - out)	activity program: graphs; drawing up a plan for a return to work	peak-stop exercise; activity program: graphs; plan for return to work
7. Changing lifestyle and relapse prevention	8, 9, 10, 11, 12, ... (through -out)	first step return-to-work plan; discussion of impeding circumstances; environmental factors; cognitions and other likely problems	activity program: graphs; steps for return to work
	13, 14, 15, 16	dealing with setbacks; preparing for therapy completion; evaluation	

Therapists, training and supervision

Thirteen psychotherapists participated in the research project 'Cognitive behaviour therapy for chronic fatigue syndrome: a multi-centre randomised controlled trial'[3]. The therapists worked at three different locations: Leiden, Maastricht and Nijmegen. The therapists were psychologists, psychiatrists or health scientists and all were qualified or assistant behaviour therapists. At the start of the project none had any earlier experience with cognitive behaviour therapy for

CFS. Prior to the start of the treatments all therapists received extensive training in the use of the manual 'CBT for CFS'. The training course comprised two two-day meetings, followed by several follow-up sessions. Preceding the training sessions all therapists had studied the treatment manual as well as literature on CFS and cognitive behaviour therapy. For the training sessions and subsequent supervisions use was made of, among other techniques, video recordings, audiotapes, fictitious problems, role-plays with simulated patients and the therapists' own cases. The in-situ supervisions were initially conducted on a weekly basis and, at a later stage, every other week. Every other month a plenary supervision was arranged to discuss those issues that had caused the therapists problems. The therapists of one of the three locations selected these topics, together with the supervisor, and they provided their own CFS cases. During these central supervisions, additionally, role-plays were practised or the supervisor raised specific points for discussion based on the experience of the preceding months. In total eight such plenary sessions were held over a period of 18 months. The main topics discussed in these sessions are listed in table 2.

Table 2

THE MAIN TOPICS DISCUSSED DURING THE PLENARY SUPERVISION SESSIONS

- How to recognize individual cognitions, define new (target) cognitions, and achieve the desired changes in cognitions (Socratic dialogue).
- How to enhance the patient's self-efficacy.
- What to do with a patient using a wheelchair.
- What to do with a patient using medication.
- What to do with sleeping problems and sleeping during the day.
- How to alternate periods of rest and activity: base level and peak-stop exercise.
- What constitutes a good activity program, and how to respond to the activity graphs.
- How to handle passive patients.
- What to do with company doctors and work-related problems.
- What is improvement, what is recovery.
- How flexible are you allowed to be with the manual.
- How to integrate individual functional analyses.
- How to integrate additional patient-specific problems and co-morbidity.
- Balancing between permissiveness and authoritativeness.
- The therapist's cognitions regarding the treatment.
- Emotions patients may evoke in the therapist.
- Resistance and motivation of therapist and patient.

Compliance with the treatment manual

To verify whether the therapists had complied with the guiding principles of the treatment manual, all therapy sessions were audio taped and analysed by an independent rater. The independent rater was a psychologist who knew the treatment protocol but was not further involved in either the treatment or the study. In total 1097 sessions were conducted. A random sample of 61 audiotapes (a good 5%) was analysed. In 49 of the cases the tapes comprised a full session. Twelve of the recordings were incomplete, mostly because the therapist had forgotten to turn the tape over after half a session, when one side of the tape was full. The manual was subdivided and scored for the following treatment aspects: cognitive restructuring, setting limits, activity program, return to work (or resumption of other personal goals), and 'other CBT'. The sessions were analysed by means of the audiotapes, their so-called verbatims, and a checklist. For each of the treatment aspects the time dedicated to this aspect during a session was noted. In addition, the checklist was used to indicate on a 5-point scale (minimal, some, reasonable, considerable, extensive) for each session how much attention the therapist had paid to the treatment aspect the manual prescribed for that session. An overall judgement on the session as a whole was given using a 3-point scale (insufficient, sufficient, good). This judgement was based on both the amount of time spent as well as the attention paid to the several treatment aspects in a session, compared with the prescription by the treatment manual.

Therapists' ratings of treatment aspects

As regards the questions about the treatment, the manual was subdivided into the same treatment aspects as used for the analyses of audiotapes. In addition, these aspects were further subdivided into subcategories (see table 3).

The therapists were asked to evaluate the CBT for CFS manual for these subcategories on a scale ranging from 1 (agree) to 6 (disagree) on the basis of the following statements:

- I can adequately apply this myself
- In my view, patients understand the rationale of this aspect well (this item was not assessed for the questions relating to 'other CBT')
- I think this is important for a successful treatment
- How this aspect is to be effected, is sufficiently described in the manual.
- Can, in my view, not be adequately applied by an untrained psychotherapist, i.e. a (cognitive) behaviour therapist working solely on the basis of the manual.

In addition, the following overall statements were included:

- CFS patients are more difficult to treat than other patients with somatic complaints
- CFS patients are more difficult to treat than patients with psychological complaints.

Similarly, these statements were scored on a scale from 1 (agree) to 6 (disagree). Answers were dichotomised in agreed (1, 2 or 3) and disagreed (4, 5, 6).

Apart from these last 2 statements, the therapists primarily used score 1 (40% of the answers). The scores 2 (26% of the answers) and 3 (17% of the answers) and 4, 5 and 6 (together 17% of

the answers) were used far less frequently. This is why, in the representation of the therapists' evaluations, we only show the percentages of score 1, reflecting the proportion of therapists who fully agreed with that specific statement.

Results

Did the therapists do what they were expected to do?

During all sessions themes were dealt with as described by the manual. In 25% of the sessions issues that were not related to cognitive behaviour therapy for CFS (other non-cognitive behaviour therapy) were raised as well. The proportion of time allotted to these non-relevant topics was, on average, 8%. The overall judgement revealed that the rater considered 87% of the sessions to be sufficient or good.

A comparison of the proportion of time to be allocated to the various aspects as stipulated in the manual with the time actually spent on these themes showed many similarities, particularly with respect to the aspects cognitive restructuring, setting limits and the activity program (figure 1). As regards the percentage of time allocated to return to work and other cognitive behaviour therapy the differences were greater. Compared with the manual, less time was dedicated to a return to work and more time was spent on other cognitive behaviour therapy.

Figure 1

PERCENTAGE OF THE TIME SPENT ON THE SEVERAL TOPICS DURING A SESSION AS PRACTISED BY THE THERAPISTS COMPARED WITH WHAT WAS PRESCRIBED BY THE MANUAL

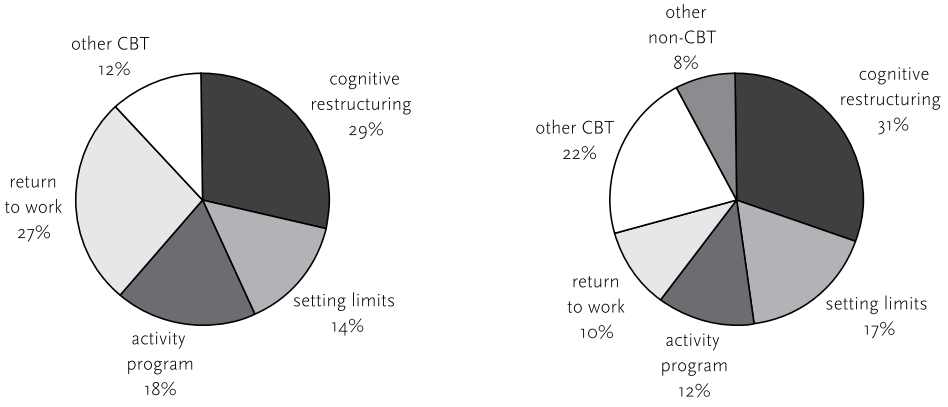

Table 3

THERAPISTS' RATINGS OF THE COGNITIVE BEHAVIOUR THERAPY FOR CFS TREATMENT ASPECTS

	Can I adequately apply	Is understood well by the patient	Is important for a successful treatment	Is sufficiently described in the manual	Cannot be adequately applied by an untrained therapist
Cognitive restructuring					
Explanation of rationale	85%	54%	100%	39%	23%
Making an inventory of cognitions	31%	8%	62%	15%	23%
Challenging cognitions	39%	8%	69%	8%	46%
Setting limits					
Explanation of limits	69%	62%	92%	46%	23%
Implementing peak-stop exercise	54%	46%	62%	15%	15%
Activity program					
Explanation of activity program	69%	62%	85%	31%	15%
Implementing activity program	46%	31%	77%	15%	23%
Return to work/Other personal goals					
Defining goals	39%	31%	77%	23%	15%
Action plan return to work /personal goals	31%	23%	62%	8%	23%
Implementing plan return to work /personal goals	31%	23%	69%	15%	31%
Other CBT					
Lack of confidence	31%		85%	8%	54%
Insufficient motivation	23%		92%	8%	46%
Integrating individual problems	31%		77%	8%	39%
Dealing with co morbidity	18%		85%	0%	31%

Which treatment aspects could be applied adequately by the therapists?

For most therapists explaining the treatment's rationale, the activity program and setting limits posed the least problems. At the stage of having the patient implement the peak-stop

exercises and activity program fewer therapists stated they could adequately apply. With respect to defining and challenging cognitions, formulating the final goal, drawing up and realizing a plan for a return to work, integrating individual problems and dealing with a lack of confidence, a third of the therapists indicated that they could adequately apply. One fifth of the therapists reported that challenging insufficient motivation and dealing with co-morbidity could be adequately applied (table 3).

Which treatment aspects were understood adequately by the patients?

The explanation of the rationale, setting limits and the activity program were, according to the therapist, best understood by the patient, followed by the implementation of the peak-stop exercise and activity program, defining targets and drawing up and executing a plan for a return to work. A mere 8% (one therapist) had the impression that the patients understood what defining and challenging cognitions entailed.

Which aspects did the therapists regard as important for a successful treatment?

For the three elements rated as the least significant still 62% of the therapists indicated this as important. Defining and challenging cognitions, implementing the peak-stop exercise, and making and implementing the plan for a return to work were considered least relevant.

What was described adequately in the manual?

Only with respect to the aspects explaining the treatment rationale, setting limits, and the activity program 31-46% of the therapists stated that these were amply described in the manual. The aspects implementing the peak-stop exercise and activity program, and also work resumption, cognitive restructuring, and the elements categorized as 'other CBT', are hardly indicated as having been adequately described in the manual.

Which treatment aspects would not be adequately applied by an untrained therapist?

Table 3 lists for each treatment aspect the percentage of therapists who thought that the particular aspect could not be adequately applied by an untrained therapist. Lack of confidence, insufficient motivation and challenging cognitions were seen by about half of the therapists as likely to pose problems for an untrained therapist.

Overall statements

Respectively, the answers of 11 and 12 therapists were available. One therapist just skipped the overall statements, one therapist had no prior experience with other patients with somatic complaints. Seven therapists (64%) indicated that they found CFS patients more difficult to treat than other patients with somatic complaints. Ten therapists (83%) stated CFS patients were more difficult to treat than patients with psychological complaints.

Discussion

As evidenced by the audiotape analyses, overall the therapists applied the treatment as prescribed by the manual and, as shown by the effect study, successfully[3]. Still, therapists found several aspects of the manual-based CBT for CFS treatment difficult to administer.

Explaining the treatment rationale and having the patients comply with their limits and activity program was managed quite well. With respect to bringing about a change in the patient's cognitions, as well as having the patients draw up and follow up on the action plan aimed at a return to work (or reaching other personal goals), already fewer therapists indicated that they could apply that adequately. Together with integrating patient-specific problems and managing a lack of confidence and motivation these aspects posed them the most problems. Particularly for co-morbidity and dealing with lack of confidence and motivation and integrating individual problems the therapists expressed the manual was not explicit. These aspects as well as challenging cognitions were also the treatment components of which was stated that these could not be easily applied without additional training in the use of the manual. Since it is difficult to describe these aspects explicitly in a manual, we feel that specifically these components of the therapy need to be mastered through training and supervision. It needs to be noted that the results as derived from the questionnaire are in line with the topics discussed in the plenary supervision sessions. These frequently involved cognitive restructuring, tailoring the program to the individual patient, and the patient-therapist interaction.

This study had several methodological limitations. For instance, since the questionnaire could only be put to the 13 therapists who had participated in the study, our sample was small. In addition, only a limited number of scores of the 6-point scale were used. This may possibly be due to the respondents' desire to give socially acceptable answers. However, the scores clearly indicated at which aspects the manual was found to be lacking. Furthermore, the responses to the various items are consistent in that they show which treatment aspects the therapists considered less or more difficult. Despite the limitations, we can say that the responses to the questionnaire constitute a useful supplement to the acquired clinical experience in the use of the manual and the associated training and supervision.

That defining and challenging cognitions posed serious problems may also be attributed to the (lack of) therapists' prior training and experience. Therapists were selected on the basis of their experience with behavioural therapy, but the extent of practical experience with cognitive therapy was not the same for all therapists. Similarly, therapeutic experience with patients suffering from somatic complaints was quite diverse and ranged from 0 to 24 years. That the

therapists indicated that putting the manual to practice had not always been easy may also be related to the version of the manual they were working with, which did not yet differentiate between passive and active CFS patients[12]. The effect study[3] had shown that the standardized treatment proved specifically suitable for the treatment of the relatively active CFS patients but hardly worked for the passive CFS patients. As passive CFS patients are characterized by a fear and avoidance of activity, complying with preset activity limits proved to be of no use to these patients. We now know that for this group the stage at which activity levels are raised needs to be brought forward.

On the basis of the experiences reported by the participating therapists, their supervisions as well as the results of the effect study, the treatment manual has been revised. The manual now makes a distinction between the treatment of passive and relatively active CFS patients. Also with respect to flexibility the manual has been modified. It is now stressed that the therapist will always need to investigate for each individual patient which the specific key factors are that maintain the complaints of this particular patient. In the course of the treatment a function analysis of the patient-specific perpetuating factors is recommended[13], in line with Schulte[14] and Davison[15]. It is our view that a treatment manual should provide insight into and contain detailed information about the function analysis of the patient group as a whole, the specific cognitions and behaviours of the patient or client population, the interventions specifically targeted at these cognitions and behaviour, likely motivational and interaction problems, as well as provide strategies, interventions and additional recommendations illustrating ways to deal with such problems. Agreeing with Heimberg[16], the difficulty is that in order to integrate the patient-specific function analysis with the manual the therapist needs to have full control over two different aspects: both the manual and the individualized treatment need to be combined. This implies that specific additional skills may be needed and that the process places high demands on basic technical and interaction skills, as well as on the preparation and evaluation of the sessions.

There has been much debate about the desirability of the introduction of research-based treatment manuals in clinical practice. Much of the debate concerned the strengths and weaknesses of such evidence-based treatments and the differences between research and practice, which have been discussed and refuted frequently[16-23]. Despite these objections many defend the notion that clinical practice should take advantage of the empirical evidence on the effectiveness of treatment procedures or manuals [19,24-28].

Working with the present evidence based treatment manual requires solid cognitive behavioural and interaction skills of the therapist, as well as a sound knowledge of the scientific state of affairs concerning CFS. Standardized, empirically validated practice does not necessarily make treatment easier, but it may at least enhance quality.

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Cognitive behaviour therapy for relatively active and for passive CFS patients

9

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Abstract

In chronic fatigue syndrome (CFS), facilitating, initiating and perpetuating factors are distinguished. Although somatic factors might have initiated symptoms in CFS, they do not explain the persistence of fatigue. Perpetuating factors make the symptoms prolong. Cognitive behaviour therapy (CBT) for CFS is focused on these perpetuating factors. Recently it has been shown that, based on their level of activity, two groups of patients can be distinguished. For so-called relatively active CFS patients the main perpetuating factors are non-accepting and demanding cognitions leading to bursts of activity. For so-called passive CFS patients the fear that activity might worsen their complaints resulting in avoidance of activity, is the most important perpetuating factor. These differences in perpetuating factors result in separate treatment manuals for relatively active and for passive CFS patients. Before describing the treatment manuals, basic assumptions, considerations before starting CBT for CFS, and ways to determine the activity pattern are outlined.

Introduction

Chronic fatigue syndrome (CFS) is characterized by a clinically evaluated, unexplained persistent or relapsing chronic fatigue that is of new or definite onset (i.e. not lifelong), lasts for at least 6 months, and that is not the result of ongoing exertion, is not substantially alleviated by rest, and results in substantial reduction in previous levels of occupational, educational, social, or personal activities[1]. Several reviews of randomised controlled trials showed that cognitive behaviour therapy (CBT) is an effective treatment for CFS[2-4].

In CFS facilitating, initiating and perpetuating factors can be distinguished. Somatic factors like viruses are often mentioned to initiate chronic fatigue. Some prospective studies showed that 10 to 17 percent of the patients with a viral infection fulfilled CFS criteria after 6 months[5,6]. However, patients without a viral infection had the same chance to develop CFS. Although there are some indications that psychosocial problems and life events initiate fatigue, convincing evidence is still lacking[7,8]. Psychosocial problems are also mentioned as facilitating factors. A prospective study showed that psychological problems are a predictor for chronic fatigue[8]. Premorbid action proneness might also facilitate the development of CFS[9]. Although little is known about initiating and facilitating factors in CFS, more evidence is found on the perpetuating factors. According to a model developed by Vercoulen and colleagues[10], a strong focus on bodily symptoms, low levels of physical activity and a poor sense of control contribute to an increase in the severity of fatigue and functional impairment. Strong somatic attributions have an indirect influence on fatigue, via lower levels of physical activity. Most factors in this model of perpetuating factors in CFS have been found in other studies as well (for example by Heijmans[11] and Wessely, Hotopf and Sharpe[12]).

The cognitive behavioural treatment for CFS is based on the model of perpetuating factors[13]. CBT for CFS is directed at decreasing somatic attributions and the patients' focus on bodily symptoms, increasing their sense of control over their symptoms, and restoring the balance in activity patterns. One of the randomised controlled trials that showed the effectiveness of CBT for CFS was the study of Prins and colleagues[14]. This study showed that the treatment manual used was not appropriate for all CFS patients. It seemed that, based on their activity level, three types of CFS patients could be distinguished: pervasively active, moderately active and pervasively passive CFS patients[15]. The protocol used in this effect study did not seem to work for the so-called passive CFS patients[14], which is about 25% of the CFS population[15]. Based on these results, the treatment manual for passive CFS patients was adjusted. The main difference is that for pervasively active and moderately active (together so-called relatively active) CFS patients,

the treatment starts with a focus on a good alternation between rest and activity. For passive CFS patients a gradual increasing activity program is started immediately in the beginning of the treatment.

In this article, first basic assumptions of the treatment and considerations before starting CBT for CFS are discussed. Thereafter, how to determine the activity pattern and the treatment manuals for relatively active and for passive CFS patients are described, followed by suggestions for relapse prevention. In conclusion, applying CBT in other than individual ambulatory adult patients or CBT for CFS by others than psychotherapists, are discussed. The general treatment outline is shown in table 1.

Table 1

TREATMENT OUTLINE

Introduction and intake

- Explanation of basic assumptions:
  - distinction between causal and perpetuating factors
  - objective is full recovery, defined in concrete individual treatment goals
- Preconditions:
  - possible co morbidity can be integrated
  - no ongoing engagement in legal procedures of disability claims
  - no concomitant treatments
- Motivating the patient: discussing attitude and expectancies
- Individualizing treatment:
  - determining and defining fatigue-related cognitions and behaviour
  - determining and defining the activity level

Treatment

RELATIVELY ACTIVE CFS PATIENTS

- Explanation of perpetuating factors:
  - non-accepting cognitions
  - activity peaks
- Challenging complaint-enhancing cognitions
- Establishing a base level
- Systematic increase of activities
  - physical activity program
  - work-resumption or achieving other personal goals

PASSIVE CFS PATIENTS

- Explanation of perpetuating factors:
  - anxious cognitions
  - inactivity
- Challenging activity-impeding cognitions
- Systematic increase of activity
  - physical activity program
  - mental activity program
  - social activity program
  - work-resumption or achieving other personal goals

Relapse prevention

- Encouraging self-activity
- Getting rid of the patient label
- Being aware of pitfalls
- Follow-up and treatment evaluation

Basic assumptions of CBT for CFS

Discussing basic assumptions of the treatment, the motivation of the patient and exploring factors that may interfere with CBT for CFS are subject of the first sessions with the patient. It is recommended to have a spouse or other partner involved in these session at least.

Distinction between causal and perpetuating factors

CBT for CFS is based on the distinction between causal and perpetuating factors. Although somatic factors might have initiated the symptoms, they do not explain the persistence of fatigue. Perpetuating factors make the symptoms endure. Therefore, CBT is focused on these perpetuating factors.

Objective of CBT for CFS

Perpetuating factors in CFS are of a cognitive and behavioural nature. Aim of the treatment is to restructure these cognitions and behaviours in such a way that the patient's complaints return to healthy proportions and that work or other normal daily activities can be resumed. Recovery is the goal aimed for. The patient describes what kind of behaviour he needs to be able to do again to consider himself a healthy person. Recovery is defined in concrete behaviour for each particular patient, leading to concrete goals for treatment. The objective of being recovered poses some extra problems. In case of disease benefits, possible negative financial aspects of recovery have to be discussed. Becoming healthy will go at the expense of disease benefits, which may intervene recovery. To prevent financial declination a paid job has to be found.
Recovery does not mean that the patient will lead the same life as before his complaints. First, premorbid activity proneness might have been a facilitating factor. Second, the patient may have an unrealistic idea of his premorbid functioning based on incorrect or idealized memories. Finally, the patient may have an unrealistic idea of what 'normal' functioning is, based on too high standards.

Before starting CBT for CFS

Before starting CBT, complaints of the CFS patient should be analysed on a somatic, cognitive, behavioural, emotional and social dimension. The somatic dimension involves questioning the patient's symptoms. What are the patient's complaints? What are the associated functional impairments? How does the patient spend his or her day and how do the complaints manifest themselves in the course of the day (description of a normal day)? Is this description exemplary of other days? In other words, are there any fluctuations in the occurrence of the complaints? When did the complaints mentioned first manifest themselves? In what way? Has the patient tried to find (professional) help? The cognitive dimension involves cognitions concerning fatigue like the patient's sense of control, attributions and his daily cognitive reaction on fatigue. Has the patient in his view been sufficiently examined physically? What are his views on what caused the complaints? Does the patient see other ways of influencing his complaints? Does the patient have a tendency to catastrophise his complaints? What views does the patient have on CFS? What is the patient's attitude regarding his complaints? What is his attitude towards a psychological intervention? The behavioural dimension concerns the patients behavioural reaction to his fatigue, including all he has done to improve his situation. What medication or diets is the patient on and what other treatments is he undergoing at this moment? What does the patient do to prevent his complaints from getting worse? What activity pattern is typical for this patient (predominantly passive; both active and passive at times, and subsequently passive; still relatively active)? What activities does the patient no longer undertake due to his or her complaints? What about the patient's sleeping pattern? Do the complaints affect the patient's concentration, memory or other mental activities? Do the complaints influence the patient's social activities? What was the nature of the patient's occupational activities? Since when has he stopped working? What type of benefit does the patient receive (social, unemployment, disability)? Is the patient involved in any legal procedures in relation to benefits? The emotional dimension involves whether the patient is for instance angry, anxious or sad about his situation. Does the patient have any feelings of anxiety that his or her complaints will get worse? Is the patient afraid to undertake activities? The social dimension involves the patient's interaction with his social environment, including spouse, family, friends, neighbours and physician(s). What effects do the patient's complaints have on his social environment? How do the patient's family members (spouse) react to his complaints? What are their ideas about the complaints? How do they react when the patient is affected by his complaints? Besides individualization, careful analysis of the patient's situation has several goals. It may reveal factors that can interfere with CBT for CFS.

Factors that may interfere with CBT for CFS

Co-morbidity

About half of the CFS patients is known with severe psychological or psychiatric co-morbidity[16]. In most cases they do not offer an explanation for the patients complaints. As in other somatic disorders, psychiatric co-morbidity in CFS is found without the existence of a specific relationship with the disorder. In case of psychological or psychiatric co-morbidity, however, it is important to examine whether there is a relationship with the chronic fatigue. If it is a consequent of fatigue it might be supposed to dissolve during treatment. If it is an antecedent of the chronic fatigue, it will be treated during CBT for CFS. If there is no relationship between the co-morbidity and the chronic fatigue whatsoever, one has to determine the most prominent problem to be treated first. If chronic fatigue sustains after adequate treatment of the co-morbidity, CBT for CFS is still initiated.

Claims for disease-related benefits

It has been found that engagement in a legal procedure concerning financial benefits predict a worse outcome of CBT for CFS[17,18]. Therefore it was stated that CBT should not be offered to CFS patients during their engagement in legal procedures of disability claims. In these procedure one has to convince the medical board of the severity of symptoms and disabilities. This is incompatible with a treatment aimed at recovery. Involvement in a procedure is carefully questioned out. Treatment only starts after the procedure is concluded. To the patient it is explained that it is hardly possible to work on recovery on the one hand and proving one's illness severity on the other hand. After completion of the procedure the treatment can start after all.

Concomitant treatments

CFS patients are actively seeking for help. As a consequence, several CFS patients use medication or have alternative medicine. Mostly without success. For CBT it is necessary not to be involved in other treatments at the same time. During CBT for CFS the patient will start to change cognitions and behaviour in order to influence his symptoms and disabilities. To see whether these changes are effective it is necessary to know to what this can be attributed to. This is impossible if more than one treatment is followed. Therefore all concomitant treatments are inventoried. With understanding for the fact that the patient tries everything to improve, it is discussed with the patient whether and, if so, at what time he is prepared to stop concomitant treatments. Only thereafter CBT will start.

Motivation of the patient: attitude and expectancies

Creating the right treatment conditions is a prerequisite for successful treatment. Establishing the patient's attitude toward CBT is essential. CFS patients often are sceptical and expectantly towards a psychotherapeutic treatment. It is therefore important to question this attitude, and to make any resistance towards CBT a subject of discussion. Their attitude may originate

from several sources. Patient organizations may spread information about CBT for CFS, often consisting of summaries of scientific studies and comments of patients. The patient is stimulated to put any resistance or doubts about the intervention forward. In case of a negative view about CBT for CFS, the patient is offered objective information about the intervention, in this way giving him the opportunity to form his own opinion. Secondly, the patient may be referred by his physician, but feels that he is not yet properly physically examined. If the patient perseveres in this opinion after explanation of the CBT treatment model, he can be given the option to go back to his physician to discuss the matter once more. To prevent excessive medical consumption, it is best first to agree about the extent in which physical examinations need to take place. Thirdly, the patient's attitude on CBT may be determined by his previous experience with psychological or psychiatric treatments. A study amongst members of the Dutch ME-association showed that more than half of them had contacted a psychologist, psychiatrist or social worker[19]. If these treatments concerned the patients fatigue, they were probably focused on better coping and not recovery. The patient is asked for his previous treatment experiences, including duration, type, content and outcome of the treatment, because they may determine his attitude and expectancies toward the current treatment. Expectancies can be adjusted by explaining the treatment model, and how psychological factors, by which thoughts, feelings and behaviours are meant, contribute to physical symptoms in general and to CFS in particular. Differences between the previous and the current treatment are stressed. To further challenge incorrect expectancies, it is emphasized that recovery is the goal of treatment and that self-activity is a prerequisite for success. It is not the intention to persuade the patient into CBT, but to give him the opportunity to form his own opinion about the treatment and whether or not he wants to go for that. The patient has to be given the time to make up his mind about the pros and cons of CBT for CFS.
Although most patients are willing to start CBT after a careful and serious approach of the therapist, some need more time to make a final decision. In some cases CBT is advised against because it is expected that CBT can not get the priority of the patient, for example in case of difficult family circumstances. However, in case the patient is not immediately starting, an arrangement is made how the patient can get back to the treatment proposition. In most cases CBT can start on a later moment with a motivated patient.

Individualizing treatment

From scientific studies perpetuating factors are known for the CFS population as a whole. For each particular patient these perpetuating factors have to be defined in individual and concrete cognitions and behaviour. Using self-monitoring, the patient examines the specific cognitions and behaviours perpetuating his symptoms and restrictions. Although this self-monitoring positively improves the patient's self-efficacy, it also strengthens the patient's focus on bodily symptoms. Therefore, if the specific perpetuating cognitions and behaviours of the particular patient are known, severity of symptoms is no longer monitored. The focus in self-monitoring will be shifted to the registration of the cognitions and behaviours to be changed, in this way

also shifting the attention to what the patient himself can do about his situation. So, self-monitoring stimulates self-activity of the patient, enables individualization of the treatment, gives part of the responsibility for a successful treatment to the patient, and, in this way, improves the patient's sense of control as well as his motivation for treatment.

Determining the activity pattern

In CBT for CFS behavioural change concerning physical activity is essential. The type of CBT the patient needs, depends on the type of his activity pattern. The activity pattern is best established using an actometer. It allows the activity levels to be determined easily and accurately[20,21]. However, many therapists do not have access to an actometer. Then the activity pattern needs to be determined by means of an anamnesis, alternatively supplemented with self-monitoring data.

Because nearly all CFS patients will claim that they hardly do anything anymore, it is important to obtain concrete information about the patients activities during a day. Talking through a normal day will allow the therapist to derive the degree and extent of the patients activities. The following questions can help determine whether the patient involved is passive or relatively active: "How much time do you spend lying down on your bed or couch each day? How often (per day/per week) do you leave the house? For how long? What is the maximum time you spend walking at a stretch?" It is clear that the patient with a low activity pattern will spend a great deal of time lying down, will not walk for long periods of time and will not go out frequently. The answers to the last two queries will also depend on the support the patient receives. Thus, a CFS patient who lives alone and does not get any help is compelled to be active to a certain extent since he needs to go out for food.

As stated above, the type of the patient's activity pattern determines which protocol will be used to treat the patient. The self-monitoring records the patient will keep can also be used to test this initial pattern and will help determine the definite pattern.

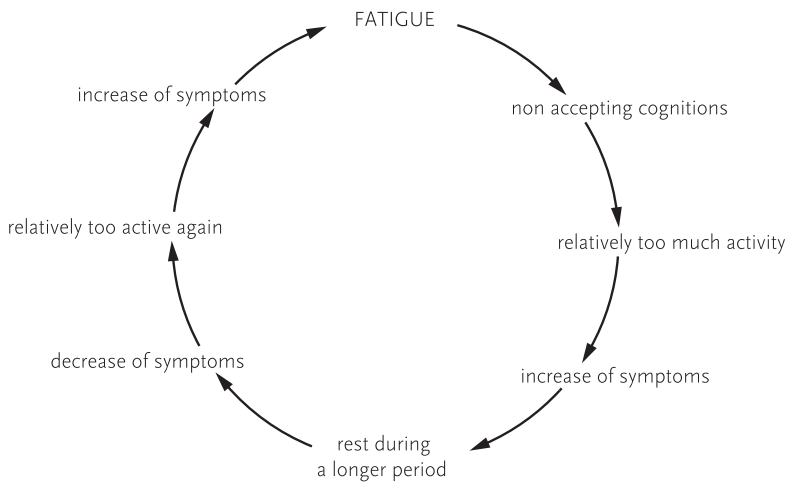
The relatively active patient

Challenging complaint-enhancing cognitions

Relatively active CFS patients often have non-accepting, demanding and therefore complaint enhancing cognitions. Fluctuations in the activity level of these patients are provoked by these cognitions. Figure 1 shows what a circle of perpetuating factors for relatively active CFS patients may look like.

Figure 1

PERPETUATING FACTORS FOR RELATIVELY ACTIVE CFS PATIENTS



Examples of complaint enhancing cognitions leading to bursts of activity are “If I give in to my complaints, I will not be able to do anything at all”, “I do not quit my activities, because if I give in to my complaints it will only get worse”, “I am a weakling if I do not stay active”, “I have to stay active because I don’t want to burden other people”. The moment the principal perpetu-

ating cognitions and behaviours of the particular patient are clear, cognitions are challenged. Hereafter a base level is established and an activity program will start. First the patient will however start with practicing more helpful accepting cognitions like "It does not make sense to keep opposing to my symptoms, I better accept them for the moment ", "It is just the way it is", "I don't have to be able to do everything, I am only a human being too", "Everyone has his limits, so do I", " I better learn to increase my activity level in a gradual and systematic way in stead of being too active followed by being fagged for a while thereafter".

Establishing a base level

For relatively active CFS patients a base level has to be established by alternating rest and activity in order to prevent bursts of activity and hereby extreme bursts of fatigue. By base level is meant: the total of activities a patient can do spread over the day without these causing extreme fatigue. The so-called peak-stop exercise can be used to attain the base level. With the peak-stop exercise the patient learns to quit his activities the moment his fatigue aggravates. For some CFS patients the negative effects only manifest themselves after they have stopped their activities or even a day thereafter. Here, self-monitoring data are used to determine a base level.

During the peak-stop exercise cognitions like "I will just finish this and thereafter I will rest" or "this has to be done before tomorrow, so I will go on to it's finished" or "I know that if I am doing to much, my symptoms will be worse tomorrow, but now I have a nice day at least" will have to be replaced by cognitions like "I better stop right now, there will be another day tomorrow and I will finish my activities then". The 'positive' cognitions the patient may have are often satisfying in the short term, but are not conducive to their symptoms and health in the long term. During the period the patient applies the peak-stop exercise it is monitored that he does not lapse into total inactivity. The exercise is about finding the right balance between periods of rest and periods of activity. It is a temporary aid, which will not be needed later on, because, as with non CFS patients, exercise peaks can than be performed without long-lasting negative consequences. Usually, patients are asked to put their base level down on paper. Which activities should be included in the base level depends on the patient's personal circumstances. Some may still be able to go out to work a few hours per day, whereas for others the base level will have been reached after they have completed taking a shower, got dressed, had breakfast and performed some domestic activities.

The patient's base level should leave some room for manoeuvre. Unexpected events or unforeseen activities – so much part of life – need to fit within the set level. In addition, the base level needs to allow room for the activity program, which will be described below.

If, after a number of sessions, a relatively active CFS patient is still seriously fatigued, has improved little since the start of treatment, an evaluation of the base level may reveal that the patient still does too much or for too long a period. The fatigue may also be explained by the way the patient goes about things, for instance a hurried, tensed or perfectionist manner. Both instances warrant special attention and need to be resolved.

Setting the base level also implies normalizing the patients sleeping pattern. Most CFS patients tend to sleep long hours, sleep and lie down frequently in the course of the day, or cannot get to sleep at night even though they are feeling extremely tired. It is essential to try and normalize the sleeping pattern of these patients as quickly as possible. This implies going to bed and getting up at fixed times and no sleeping during the day. For patients who still work (part-time), it needs to be established to what extent the job can be fitted into the base level. Together with the patient the compatibility of the (part-time) job with the patient's base level is judged. If work does not involve that the person's limits are exceeded, it may be useful to have him continue working, since this provides an opportunity to evaluate the way the individual goes about his tasks. Is the patient always pressed for time, always busy; is there hardly any time for a break? Decide, together with the patient, whether his or her work approach is adequate or whether it needs to be adjusted.

It may also be useful to discuss with the patient the possible consequences this base level may have on the patient's environment. The patient may no longer meet (presupposed) requirements and no longer lives up to expectations. Generally, the best way to resolve this matter is to involve those in the patient's environment in the treatment and to jointly try and find (temporary) solutions to any emerging problems. Temporarily involving the patient's spouse or others may significantly help the patient to comply with his base level.

Increasing activity

Activities can be divided into three categories: physical, mental and social. In nearly all cases treatment starts with a physical activity program. For relatively active CFS patients this mostly suffices to be able to start work-resumption or achieving other personal goals here after. The moment the patient has set his base level, the physical activity programs starts. The patient selects a simple physical activity that can be performed every day, the duration of which can be conveniently recorded. The aim is to have the patient gradually and systematically increase the frequency or duration of this particular activity. Walking and cycling are generally good examples of such an activity. Directive for relatively active CFS patients is to perform an activity like walking or cycling twice a day, starting at a level of which is certain that symptoms do not aggravate. Mostly this is five to ten minutes. The activity level is increased with one minute a day for each time the activity is performed. A minimal increase of five minutes a day is agreed upon, giving the patient the opportunity to skip the activity once or twice or to refrain from raising the walking or cycling time. Although the activities that fit in the base level will expand, alternating rest and activity stays important.

The patient is asked to indicate the actual duration of each activity on a graph. By analysing stagnations in the activity program impeding cognitions or difficulties the patient might have with respecting limitations can be traced. The most common problem with the relatively active CFS patients is that they increase their activity level too fast, eventually resulting in an increase of symptoms. Another rising problem might be that the activity program is not systematically

and consequently or to slowly performed. In these cases the activity program may not have the priority of the patient while other daily activities are performed too often or for a too long duration. By means of the activity program patients also learn to prioritise. This is accompanied by a cognitive change essential for a successful treatment outcome. The cognition "quickly doing this or that" is replaced by "gradually and systematically increasing activities".
In general the activity program will end at a maximum of 60 minutes of walking or cycling. By that time most patients will have become aware of the fact that they are capable of doing more without experiencing extreme fatigue and that they recover faster than before. The original base level has by then already been automatically enhanced. Gradually, walking or cycling is now being replaced by other activities. One might also choose to systematically expand mental and social activities, preparing the patient for a return to work or other personal targets.

It needs to be noted that the activity program of the relatively active patient is not about improving their physiological condition since, as far as is known at present, these patients are not deconditioned in a physiological sense[22]. The focus of the activity program is a gradual and systematic increase in activity. The fact that patients experience that they are capable of achieving this goal – if approached in the right way – enhances their sense of control and helps bring about a positive self-efficacy.

Work-resumption or achieving other personal goals

In accordance with the ultimate objective of the treatment, work-resumption or achieving other personal goals is subject to discussion from the start of treatment. In the first sessions the work situation is analysed. This involves the possibility to return to the old workplace, financial consequences of recovery, as well as whether the patient wishes to get back to work in case of recovery. Thereafter a plan for work resumption or achieving other personal goals is set up. Three steps are described. First the final goal is determined. Which work activities does the patient want to be able to perform again, which will also allow him to perceive of him as healthy? Secondly, it is formulated which working activities fit in the current base level. What is the patient capable of at this moment without resultant complaint-enhancing effects? Finally the work resumption plan is drawn up. How can the patient build up his activity level from the current situation to the ultimate goal without negatively affecting the symptoms? The patient is asked to commit the various steps to paper, taking into account any problems that may arise. Compliance with the activity plan is evaluated.
The work resumption plan is delineated by a gradual and systematic increase of working hours as well as tasks to be performed. Successful work resumption is only possible if it is also presented to the patient's employer, company doctor and/or medical adviser of the insurance company. This is preferably done by the patient himself.
When a return to work is not an option, an action plan is drawn up stipulating how to achieve other personal targets. Principles used are the same as for planning and achieving work resumption.

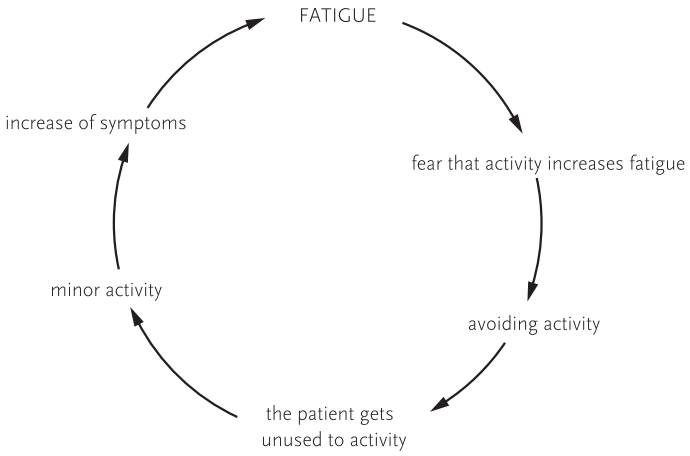
The passive CFS patient

Challenging activity-impeding cognitions

For passive CFS patients the fear that activity enhances symptoms is essential. As a result activities are avoided as much as possible. Because the body gets unused to activity, symptoms will emerge at increasingly lower levels of activity. In this way a self-fulfilling prophecy is established. Figure 2 shows a conceivable perpetuating circle for passive CFS patients.

Figure 2

PERPETUATING FACTORS FOR PASSIVE CFS PATIENTS



The aim of restructuring anxious cognitions is decreasing the fear of activity and motivating the passive CFS patient to start and sustain the activity program. Essential activity-impeding cognitions may be "As soon as I start feeling tired or start having pain I have to stop everything I'm doing " or "I can't do anything on my own anymore, others have to help me all the time". More

helpful cognitions are: "If I completely adapt to my symptoms I only make my situation worse", "By raising the level of my activities step-by-step, I will be able to push my physical capabilities further"; "If I get complaints by being active it doesn't necessarily mean that I should stop doing what I'm doing; it's just a sign that it has been some time since I've been active and my body simply needs to get used to it again; the only way to break through is by becoming active again". The patient may be requested to keep a record of his cognitions.
Compared to relatively active patients, it is generally more complicated to challenge the cognitions of these passive patients without also involving behavioural change. This is the reason why, with these patients, the moment of transfer to the graded exercise program is brought forward.

Increase of activity

Before starting the activity program, a (gradual) cessation of the use of any aids like a walking stick or wheelchair is realized. Such aids tend to obscure the patients symptoms and impairments and may undermine the confidence-building process that allows the patient to believe in his own ability to recover. After all, a wheelchair does not allow the patient to independently perform the steps of the activity program. Usually, cessation of the use of aids can be accomplished by simply explaining the situation and having the patient agree not to use the aids. If the patient wants to gradually reduce the use of the walking stick or wheelchair, this requires a concrete plan of action, indicating the time-scale, e.g., a maximum of two to three weeks. Even though cessation of the use of the aid is likely to result in an even further decrease of activities, starting the activity program at this lowered base level offers the better prospect.
Because passive CFS patients are hardly active anymore, they start their activity program as soon as possible. Most of them will choose walking as a building up activity. The directive here is to start with a one-minute walk six times a day. Every day the walking time is increased with one minute. So, for example, the first day the patient has six one-minute walks, the second day six two-minute walks, the third day six three-minute walks and so on. A total building up of five minutes a week for each walk a day is aimed at, allowing the patient to skip a day or to refrain from raising the duration. Having the activities reflected in graphs, the patient can give himself positive reinforcement about his progress. Furthermore the graphs are used during therapy sessions to detect problems in the activity building. The most common problem for passive CFS patients is that the building up process is going to slowly because of the fear that activity is harmful. The program will however need to convince the patient that physical complaints should not be taken as a sign to stop the activities. It is explained to the patient that it is obvious that, after a long period of inactivity, his body has to get used to activity again. It is important to point out that a one-minute raise is absolutely safe and that there is no danger whatsoever, nor any over taxation. It is emphasized that by this small but gradual increase, barring exceptional circumstances, a great deal of progress can be made in only a few weeks time. It is common to cut back the frequency of the walks from six times a day to two or three times a

day after several weeks. Even before reaching a certain level, for instance a twice-a-day 60-minute walk, the patient will already find that he is now also able to undertake other activities. By then the patient will also have noticed that recovery from an activity is much faster. Because passive CFS patients are inactive in every area, a mental activity program is started rather soon as well. Mental activities concern reading, watching television, doing puzzles or computer work. Usually this kind of activities are started in units of five minutes three to four times a day. Based on the same principles, a social activity program is started shortly thereafter. Here activities as making telephone calls, receiving or paying visits, or making other social calls are involved. Since the social activity program will also affect the patient's environment, the patient needs to inform others of the program. The patient decides on the content of the information. The physical, mental and social activities chosen are geared to the activities needed in the plan for work resumption or achieving other personal goals.

Frequently, passive CFS patients have rallied the support of a considerable number of people. It is also common for the patient's environment to be just as concerned and anxious as the patient. This may contribute to the complaints being maintained. If this seems to be the case the spouse or another key player from the patient's environment should be invited to attend a session to discuss how to cut back the support given.

Work-resumption or achieving personal goals

As for the relatively active CFS patients, a plan for work resumption or achieving other personal goals is made. Here, activities previously performed during the mental and social activity programs, are used as first steps towards work-resumption or achieving other personal goals.

Relapse prevention

Encouraging self-activity

In order to prevent a relapse it is paramount that the patient's self-activity is enhanced in each phase of the treatment. Will the therapist initially challenge the patient's cognitions, introduce helpful cognitions and moderate behaviour or teach the patient the necessary skills, during the course of the treatment this role will increasingly become smaller and the therapist will take more of a back seat. After six to ten sessions the therapist's role will mainly be supportive in analysing recovery-impeding factors and reinforcing goal-directed steps. By increasingly making it the patient's own responsibility to detect and anticipate difficulties and to find solutions, the patient's sense of control will be enhanced and somatic attributions will be reduced. The patient, who by this time no longer is a patient, has learned how he can influence his complaints.

Getting rid of the 'patient label'

Many patients find it hard to stop seeing themselves as patients. The term chronic fatigue syndrome already seems to suggest that having been diagnosed with CFS implies a permanent condition. The fact that many CFS patients have been suffering from symptoms for quite some time before they are referred for CBT does not contribute to their developing an optimistic outlook as far as a full recovery is concerned. In addition, patients who are referred to a psychotherapist for CFS, generally assume that they will learn to cope with their complaints rather than that they will learn to perceive themselves as healthy individuals again. This is why this should be one of the first points on the treatment agenda. In the final phase of the treatment this point is raised again when the patient is asked what he thinks still needs to be done before he can replace the marker reading 'patient' by a label indicating 'healthy'. The response of healthy individuals who are suffering from all kinds of flu-like symptoms will be quite different from the reactions of CFS patients, who, when they are incidentally experiencing complaints again, will usually interpret signals from the body as symptoms of CFS in stead of normal and temporarily fluctuations of the body.

Being aware of pitfalls

The moment the patient is feeling better, the necessity to apply the newly learned cognitions and behaviours seems no longer present. The previously used cognitions and behaviours may however be pitfalls for relapse. Within the framework of relapse prevention, conceivable pitfalls for the particular patient are detected and it is discussed how to anticipate on them. It

might be useful to let the patient write down some helpful cognitions and behavioural rules he can rely on.

Furthermore, every patient has his own specific lifestyle. Some will have difficulties with communicating their limits to others, others may be perfectionists. There are also patients who have such an intense fear of failure that they will be extremely apprehensive about achieving the treatment goals and will consequently drop out of treatment at an early stage. To prevent relapse, the patient is advised to pay specific attention to his known weaknesses. Different lifestyles may either induce the patient to do too much or too little. Both behaviours may elicit that the patient once more ends up in a downward spiral. By helping the patient to become conscious of these innate weak spots, he may prevent a relapse or learn to resolve the situation in time.

Follow-up and treatment evaluation

Treatment will usually consist of ten to a maximum of twenty sessions, also depending on the therapist's experience with the treatment. After completion of the actual treatment, follow-up sessions are conducted with the single purpose of monitoring whether the treatment effect is sustained. The purpose of the follow-up sessions is to discuss with the person involved, the 'ex-patient' now, how he has dealt with fatigue. Has he learned enough to tackle any recurring symptoms? Here, the follow-up sessions mainly take the shape of revision lessons or a refresher course. The therapist reinforces the ex-patient's positive approaches towards fatigue or his behaviours that help prevent extreme symptoms. Far better still, the therapist should have the ex-patient reinforce himself and thus help to establish a positive sense of control. It is also recommended to go through all the positive effects of the treatment once more since most patients who have been successfully treated will still report feeling tired frequently, although this no longer takes extreme forms and recovery occurs more quickly. In other words, the fatigue has been normalized. Concomitant complaints like muscle pain or joint-ache will usually already have disappeared gradually in the course of the treatment.

In conclusion

CBT for CFS as described in this chapter has initially been developed for and tested with adults. CBT is also considered suitable for the treatment of young CFS patients, provided that their individual circumstances are taken into account. Participation of the parents in their child's treatment is a precondition. In an uncontrolled study Chalder, Tong, and Deary[23] examined the effectiveness of CBT family therapy for 11-18 year olds. They found 15 of the 23 enrolled patients improved at six month follow-up.

CBT for CFS can also take the form of group therapy. In our centre several CFS patients were treated in a group setting[24]. Patients may have a good example from the progress the other members of the group are making. Comparing and discussing the participants' individual actometer patterns may help patients to get an idea which direction their activity program should take. Although group therapy for CFS has not yet proven to be effective, it seems most suitable for patients whose functional impairment is moderate.

A certain number of CFS patients may also be treated with elements of CBT by their family physician. It seems wise to select those CFS patients who are most likely to benefit from the treatment. This will usually imply CFS patients who are still relatively active and for whom the majority of prognostic factors are favourable, that is no co-morbidity, a predominantly positive self-efficacy regarding the symptoms, moderate somatic attributions, no repetitive use of medication, and a social environment that has a positive attitude toward the chances of the patient's recovery. Unfortunately, as yet there is only one study in which general practitioners were trained to deliver CBT, but the study suffered from poor recruitment and high drop out, and the treatment had no effects on the patients with CFS[25].

In the studies described earlier, therapies provided were always on an outpatient basis. Chalder, Butler and Wessely[26] reported an uncontrolled study involving six inpatients of a clinic specialized in the treatment of CFS. They provide a comprehensive description of the treatment they developed for their patients, whose severity of symptoms necessitated inpatient treatment. Five of the six patients showed considerable improvement, and this effect was still present three months after their release from the clinic. Cox and Findley[27] also described CBT and graded activity of CFS patients in an inpatient setting. They claimed at 6 months post-discharge a perceived increase in level of ability in 82% compared with prior to their admission to hospital.

It has been shown that behaviour therapists find CFS patients hard to treat[28]. Many problems therapists encounter during CBT for CFS involve the interaction with the patient. Especially moti-vating the patient for treatment, handling co-morbidity, and realizing work-resumption is

found difficult. These problems can best be dealt with by individualizing the treatment, which involves making the specific perpetuating factors of this particular patient concrete and integrating co-morbidity as it may be part of the perpetuating factors. It is recommended that therapists willing to treat CFS patients take knowledge of the current scientific state of affairs into CFS, and are experienced in CBT as well as treating patients with (unexplained) physical symptoms.

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General discussion

10

General discussion

In this final chapter our results will be summarised and the consequences of our findings for the treatment of CFS patients will be discussed. Ideas for future research will be put forward.

CFS put on the Dutch map

One aim of this thesis was to examine the prevalence of CFS in the Netherlands. Based on GP reports, an estimated prevalence of 112 CFS patients per 100 000 inhabitants was found (***chapter 2***). These results were confirmed in another Dutch study[1]. Our prevalence study was repeated in 1999[2]. This time a prevalence rate of 195 per 100 000 was found. Rather than the prevalence of CFS being increased, it is more likely to be an effect of CFS becoming better known. The skewed distribution of the reported number of CFS patients in each general practice suggests that GP reported prevalence of CFS highly depends on a GP's attitude towards CFS. Whereas 13% of the respondents stated they had no CFS patients in their practice, the mean number of CFS patients in each practice was 4.9. In our first prevalence study 27% of the GPs stated they had no CFS patients in their practice and the mean number of CFS patients in each practice was 2.8. In both studies differences between GPs in the number of CFS patients reported were obvious. A study by Prins and colleagues on the attitude of Dutch GPs towards CFS showed that half of them were reluctant to diagnose CFS, and 20% of these GPs did not accept CFS as a diagnosis[3]. Only 10% of the GPs felt capable of giving sufficient information to CFS patients. These results raise questions about the GPs' adequacy diagnosing CFS. It is not desirable that acknowledgement of the diagnosis CFS depends on the GP a patient is consulting. Especially since a GP can play an important role in CFS. If GPs diagnose CFS and acknowledge the patient's complaints, further medicalisation can be prevented and ways for better management can be discussed[4]. For this purpose, recommendations for diagnosing and managing chronic fatigue in general practice have been published[5-6]. Anyhow, based on our prevalence study an estimate of the prevalence of CFS in the Netherlands could be made. Furthermore, we seemed to have reached our aim to inform GPs about CFS. It surely helped to put CFS on the Dutch map.

Hyperventilation and physical fitness are no perpetuating factors in CFS

After we had examined the GP-reported prevalence of CFS, hyperventilation and physical fitness were studied as possible perpetuating factors (***chapter 3*** and ***chapter 4***).

Hyperventilation is a respiration that exceeds metabolic demands, immediately resulting in a decrease of arterial pCO_2 and leading to an increase of pH in the blood (alkalosis). In

Hyperventilation Syndrome (HVS), hyperventilation is held responsible for several somatic symptoms. Because fatigue seemed to occur in many HVS patients and hyperventilation in CFS patients, we hypothesised that hyperventilation could contribute to fatigue in CFS. In our study 59% of the CFS patients fulfilled symptom criteria for HVS and 59% physiological criteria for hyperventilation. However, no significant differences between CFS patients with and without hyperventilation were found for severity of fatigue, impairment, number of complaints, activity level, psychopathology and depression. It seems that hyperventilation is not responsible for the symptoms in CFS. We concluded that hyperventilation is not a perpetuating factor in CFS but an epiphenomenon. To date, no more studies on CFS and hyperventilation have appeared.

The assumed role of physical fitness as a perpetuating factor in CFS is complicated. Many treatment manuals are based on the idea - first published by Wessely and colleagues in 1989 - that a low level of activity, and consequently an assumed physical deconditioning, is the main perpetuating factor in CFS[7]. Studies on the effect of graded exercise in CFS, based on this concept of physical deconditioning, showed a treatment effect[8,9]. These study results suggest that CFS patients just have to become more active again and improve their physical fitness. This idea, however, may be disputed. The first argument stems from our own study on physical fitness. It was found that CFS patients had the same physical fitness as their healthy controls. The only differences found were that CFS patients considered themselves fatigued and quitted the exercise test at a lower level of exertion (that is: had a reduced exercise capacity), without a physiological reason. The second argument comes from the randomised controlled study of Fulcher and White[8]. They found that a decrease of fatigue and impairment after graded exercise was not correlated with physiological improvement. In an additional study, using the patients of this same graded exercise trial, the physiological response to exercise in CFS was explored further[10]. As in our study, it was found that although CFS patients were equally unfit as sedentary controls, only CFS patients had a reduced exercise capacity. They quitted the exercise test earlier than controls and perceived greater effort during exercise. It was also found that improved physical fitness after graded exercise was associated with increased capacity on the exercise test. A relation with fatigue and impairment, however, was not mentioned[10]. In the randomised controlled study of Wearden and colleagues there was a weak but significant correlation between improved fatigue after graded exercise and improved functional work capacity (the amount of oxygen consumed in the final minute of exercise)[9]. According to the authors their results suggest an improvement of the subjects' tolerance to exercise rather than a substantial increase in cardiorespiratory conditioning. It is their view that graded exercise may work by providing the reassurance to patients that activity need not cause an exacerbation of fatigue symptoms. Anyhow, it is well known that exercising improves physical fitness. There is, however, no evidence that improving physical fitness is essential in the treatment CFS and decreases fatigue and impairment in daily life. Still, one objection can be made. Van der Werf and colleagues found that, based on their activity level, a subgroup of about 25% pervasively passive CFS patients can be distinguished[11].

These patients have an activity pattern not prevalent in healthy controls, and are characterised with more severe disability compared to other CFS patients. The protocol used in our individual CBT study did not work for these passive CFS patients (***chapter 7***). Therefore we decided to immediately start with an activity programme for this subgroup. It is likely that pervasively passive CFS patients have a lower physical fitness compared to other CFS patients and healthy controls. Although it is thinkable that an assumed decreased physical fitness in this subgroup of patients is an epiphnomenon, it might be worthwhile to study the role of fitness as a process variable in the treatment of pervasively passive CFS patients.

Essentials in CBT for CFS

Our individual cognitive behaviour therapy (CBT) for CFS proved to be an effective treatment (***chapter 7***). The effect of individual CBT for CFS has also been shown in several reviews of randomised controlled trials[12-14]. We could not prove cognitive behaviour group therapy (CBGT) to be effective for CFS (***chapter 6***). Methodological issues have been discussed in the chapters concerned. Now what is essential in CBT for CFS will be reflected on. First we pay attention to 'What makes CBT for CFS effective?', discussing, among other things, the role of activity. Thereafter the question 'In what way is CBT for CFS effective?' will be dealt with, discussing different forms of CBT for CFS, among which CBGT, and the use of the manual. Finally we consider 'For which patients is CBT for CFS effective?', discussing the necessity of defining subgroups of patients and the applicability of our CBT for CFS manual to the treatment of fatigue in other conditions and to the treatment of other unexplained somatic symptoms.

What makes CBT for CFS effective?

An activity programme is an important ingredient in both graded exercise and CBT. But if improving physical fitness is not the working mechanism, then what is essential in these treatments?

From several controlled studies, comparing CBT with relaxation[15] or social support (***chapter 7***), it can be concluded that it is not just the attention received. Deale and colleagues suggest that the working element is the behavioural change common to cognitive behaviour and exercise therapies that produces a cognitive shift away from fear and avoidance[16]. Although the rationale for cognitive behaviour therapy is a fear avoidance model and exercise therapy is based on a physiological model of deconditioning and decreased fitness, both rationales lead to the use of an activity programme as an essential factor in treatment.

Effective treatments have in common that they offer a rationale that makes improvement or recovery possible, and set a goal for improvement or recovery. Such a rationale may challenge cognitions about the progress that can be made as well as about the chronicity of symptoms. Aiming for improvement or for recovery, however, is importantly different. Aiming for improvement suggests that patients will keep on having CFS, and just learn how to cope with their fatigue. Aiming at recovery induces the cognition that cure is possible. This may also partly explain

why our group therapy, aiming at coping with CFS, was not effective, where our individual CBT, explicitly setting recovery as a goal, was.

A rationale might also challenge the fear that activity is harmful. Using graded activity and experiencing that activity is not harmful may challenge the fear that activity is harmful even more. Studies showing that activity is safe and that CBT and exercise are effective in CFS may help to produce important cognitive changes and underline (parts of) the rationale given in these treatments (***chapter 5***). Deale and colleagues show that fear of activity and the belief that activity should be avoided are important to be challenged in CBT[17]. They found that beliefs about avoidance of exercise and activity only decreased after CBT, and that this change was associated with improved outcome. In line with this, Sharpe and colleagues[18] found that avoidance of activity was reported less after CBT than before. Also, avoidance of activity decreased more through CBT than through medical care. Whether these changes correlated with treatment outcome was not reported. The importance of fear of activity, as a cognition producing low levels of activity, is underlined by a study of Silver and colleagues[19]. They found that behavioural persistence to ride an exercise bike for as long as one felt able to did not correlate with maximal heart rate or resting heart rate, level of tiredness, symptom severity, illness identity or emotional distress, but with a fear of physical movement and activity. In contrast to the individual CBT studies, in our CBGT study, beliefs that activity should be avoided increased after CBGT (***chapter 6***). In the wait list condition there were no changes. This may, however, be due to the manual used in that study. Establishing a baseline - and thus decreasing activities in some ways - was stimulated before an activity programme was started. Finally, fear of activity may be most prevalent and important for passive CFS patients. Until now, studies on this subject did not differentiate between passive and relatively active CFS patients.

Looking at our model of perpetuating factors, one would expect changes in somatic attributions, self-efficacy and focussing on bodily symptoms to be important working elements in CBT as well[20]. Deale and colleagues found that physical illness attributions did not change with treatment, and were not associated with poor outcome, neither in CBT nor in the control group[17]. Sharpe and colleagues did find a decrease in physical attributions, changing more with CBT than with medical care[18]. Whether these changes correlated with treatment outcome, was not reported. In our CBGT study, physical attributions were diminished after CBGT but not in the wait list condition (***chapter 6***). A difficulty with measuring physical illness attributions is that physical attributions concerning the cause of CFS should be distinguished from physical attributions concerning the perpetuation of CFS. Although physical factors may have initiated CFS, there is no reason to believe that they have a perpetuating role. In the several studies this distinction has not been made. It will be clear that causal somatic attributions do not necessarily have to be changed after CBT.

In our CBGT study, self-efficacy and focussing on bodily symptoms remained unchanged in both groups. In other CBT trials these variables were not studied as process variables. In our individual CBT trial it was found that a higher sense of control predicted more improvement, whereas focussing on bodily symptoms predicted less improvement (***chapter 7***). These findings

led us to change the manual. Paying more attention to these process variables during treatment may lead to even better results of individual CBT for CFS.

The role of physical activity re-examined

Although all effective treatment studies in CFS have a programme to increase activity, none reported an actual increase in the level of physical activity after treatment. In most studies levels of activity are measured with questionnaires. As we know from an earlier study, most of these measures do not assess actual behaviour but cognitions about behaviour[21]. In our individual CBT trial, the actometer (a behavioural measure of actual activity in daily life) was merely used as a predictor. Only the case study of Prins and Bleijenberg showed an effect on the actometer after CBT[22]. One might wonder whether an increase in the actual level of physical activity can be expected for all CFS patients. Surawy and colleagues suggested that complaints of CFS patients were perpetuated by bursts of activity on the one hand and avoidance of activity on the other[23]. Non-accepting cognitions lead to bursts of activity, the idea that activity is harmful leads to avoidance of activity. Although there are more explanations possible for the minimal effect of CBGT, our manual, based on this idea, did not work very well in CBGT. Based on the finding that avoidance of activity had increased through CBGT, finding a balance between bursts of activity and avoidance of activity remained part of our treatment, but the graded activity programme was more accentuated and put forward. Now we know that the manual used in the individual CBT study, was only suitable for the relatively active CFS patients, and not for the so-called passive CFS patients. As described in ***chapter 9***, we therefore developed a distinct treatment protocol for passive CFS patients. For the latter group finding a balance between rest and activity was left out and the treatment immediately starts with an activity programme. It is presumable that for this pervasively passive subgroup of CFS patients the level of physical activity needs to be increased after treatment, whereas for the other patients an increase of physical activity might not be expected. As Van der Werf and colleagues found, 75% of the CFS patients have an activity pattern also present in healthy controls[11]. For these relatively active CFS patients mainly their cognitions about their level of physical activity or their regulation of activities may need to be changed. Van der Werf and colleagues also found that CFS patients as a group showed longer periods of rest following their activity peaks and patients were characterised by a larger drop in activity during the hour after the peak, than healthy subjects[11]. This finding is in agreement with the theory of Surawy and colleagues[23] and with the basic assumptions of our treatment manual currently being used for the relatively active CFS patients, underlining the importance of activity regulation.

In what way is CBT for CFS effective?

Different forms of CBT for CFS

Although individual CBT for CFS has been proven to be effective (***chapter 7***), that was not the case for CBGT (***chapter 6***). For this various explanations have been given. Cognitions that activity should be avoided were increased because of too much emphasis on rest and relaxation,

before starting an activity programme. Applying CBGT for CFS might also have been too difficult for inexperienced therapists. Furthermore, CBGT may only be suitable for a subgroup of patients. CFS patients with less severe complaints seemed to profit most from CBGT. Future studies will have to reveal whether CBGT for CFS can be effective for subgroups of CFS patients.

Some uncontrolled studies on the feasibility and effect of forms of CBT for CFS other than ambulatory individual therapy show positive results. These reports concern CBT in an inpatient setting[24-25], CBT as part of a multidisciplinary intervention[26] and CBT in a general hospital setting[27]. Some CFS patients with for example extremely severe complaints, may benefit more from an inpatient or a multidisciplinary treatment, while for others a self-help programme may be sufficient. Finally, Powell and colleagues proved that even a minimal intervention, consisting of only two individual treatment sessions and two follow-up telephone calls supported by a comprehensive educational pack, was effective[28]. Although only one experienced therapist carried out this intervention, this finding is promising. More research is needed to establish if different forms of CBT for CFS will be effective for specific subgroups of patients.

How to use the manual?

As stated in ***chapter 8***, standardised, empirically validated practice, written down in a manual, does not necessarily make treatment easier to conduct for the therapist, but may enhance its quality and effectiveness. For over 25 years there have been manual-based psychotherapy treatments, for both research purposes and training and practice[29]. The report of the Task Force on Promotion and Dissemination of Psychological Procedures of the American Psychological Association (APA) in 1995 was the start of a debate on the desirability of research-based treatment manuals in the clinical practice[30-43]. Much of the debate concerned the strengths and weaknesses of such evidence-based treatments and the differences between research and practice[32,41-43]. The discussions revealed that the resistance to the use of standardised treatments was highest under psychotherapists working in clinical practice. It was objected that the implications of the differences between client and therapist characteristics, the role of non-specific factors and the necessity to adjust the therapeutic interventions to the client's (or patient's) specific complaints were not sufficiently taken into account[34]. More arguments challenging standardised treatments included: their failure to take into account co-morbidity and the more complex problems of the clinical practice; their lack of flexibility and adjustability preventing customisation; the idea that patients or clients are not served adequately by a standardised treatment; their failure to do justice to the role of the holistic theory and function analysis; their negative effect on the patient-therapist relationship; their negative impact on the competency and work satisfaction of the therapist; and their poor practicability[32,37,39-41]. The debate on the pros and cons of standardised treatments in clinical practice has also yielded suggestions as to the desired content of such a treatment manual. Many of these suggestions underpin the importance of a manual that leaves room for customisation and flexible application[31,43-47]. As a result

of our experiences with the manual and the outcome of the therapists' adherence and perceptions study (***chapter 8***), our manual was adapted (***chapter 9***). The treatment manual provides insight into and contains detailed information about the function analysis of CFS patients, as well as the accompanying interventions and difficulties. Yet, the manual needs to be individualized. In the course of the treatment making a further specified function analysis is recommended. Agreeing with Heimberg[37] we stated that combining the manual and the individualized treatment implies that therapists may need additional specific skills and that the therapeutic process places high demands on the therapist's basic technical and interaction skills. Hopefully, our view on how to use a treatment manual will challenge dismissive cognitions therapists in clinical practice have about an evidence-based treatment manual.

Who can use the manual?

In our studies only behaviour therapists performed CBT for CFS. The therapists involved in our individual CBT study reported that in their experience treating CFS patients had been more difficult than the treatment of patients with a different somatic symptomatology or patients with psychosocial or psychiatric problems (***chapter 8***). Therapists who had little experience in treating patients with somatic complaints turned out to have difficulties in preventing patients from dropping out[2]. As we stated in ***chapter 8*** and ***chapter 9***, it is our view that therapists willing to treat CFS patients must be knowledgeable about the current scientific state of affairs of CFS, and be experienced in CBT as well as treating patients with (unexplained) physical symptoms.

One might wonder whether other than behaviour therapists, for instance GPs, can deliver CBT-like interventions for CFS. Studies on this topic are not yet available. A randomised controlled trial on the effect of GP delivered CBT for unexplained fatigue among employees did not show any effect[48-49]. In a study on reattribution for somatisation, conducted by GPs in general practice, some improvement was found. However, this was a much less complicated intervention aimed at increasing subjective health and reducing medical consumption[50]. Concerning CFS, it is conceivable that GPs will be able to treat those patients that are most likely to benefit from CBT. This will imply CFS patients for whom the majority of prognostic factors are favourable, that means who are still relatively active, have no co-morbidity, a positive self-efficacy regarding the symptoms, moderate somatic attributions, no repetitive use of medication, and a social environment that has a positive attitude toward the chances of the patient's recovery[51]. It still needs to be studied whether GP delivered CBT for this subgroup of CFS patients can be effective indeed.

For which patients is CBT for CFS effective?

In trials on individual CBT for CFS it was found that engagement in a claim for a disability-related benefit during CBT, a lower sense of control, a passive activity pattern and focussing on bodily symptoms predicted less improvement after CBT (***chapter 7***)[52-53]. Treatment outcome was not influenced by current or lifetime psychiatric diagnoses[53]. Bentall and colleagues found that poor

outcome was predicted by membership of a self-help group, being in receipt of sickness benefit at the start of treatment and dysphoria[54]. Based on these study results, it is recommended that CFS patients involved in a claim for a disability-related benefit should not be included in CBT. The other factors found to influence CBT outcome may have consequences for the treatment and for the difficulty to treat these patients in the first place.

Generalising CBT for CFS to the treatment of fatigue in other conditions

One may wonder whether our treatment manual can be effectively used for the treatment of fatigue in other than CFS cases. There are arguments that this is not the case. The manual is based on perpetuating factors specific to CFS. It has been found that the model of perpetuating factors in CFS did not fit for fatigue in multiple sclerosis[20]. A newly developed model revealed that in multiple sclerosis emotional instability, neurological impairment, helplessness and depressive mood perpetuate fatigue[55]. Studies on fatigue after cancer showed that for patients still being fatigued years after successful treatment of cancer, other factors seem to determine fatigue. Not only a low self-efficacy, lower levels of physical activity, strong causal attributions and a high tendency to focus on bodily symptoms seemed to be important, but also elevated feelings of anxiety, serious limitations in role functioning, sleep disturbances, low optimism and the acceptance of having been confronted with cancer[56-61]. Based on these perpetuating factors a CBT manual for fatigue in disease-free cancer patients has been developed[62]. A study on the effect of this treatment is currently being performed.

Generalising CBT for CFS to the treatment of other unexplained somatic syndromes

In this thesis the overlap between symptoms in CFS and in other unexplained somatic syndromes has been mentioned several times. Wessely and colleagues[63] have stressed similarities between syndromes such as chronic fatigue syndrome, premenstrual syndrome, irritable bowel syndrome and various pain syndromes. Their arguments mostly concern an overlap on a symptom level. Furthermore, they argue that CBT is superior to minimum care for most of the syndromes in which this approach has been assessed. However, it is important to notice that not all CBT treatments are the same. CBT needs to be directed at the perpetuating factors specific to each syndrome. Before treatments can be generalised, studies on similarities and differences of the perpetuating factors in these syndromes will have to be accomplished.

Future directions summarised

The distinction between passive and relatively active CFS patients turned out to be very important in the treatment of CFS. This has raised several new questions that need to be answered. One may assume that passive CFS patients, with an activity level not occurring in healthy controls, differ from healthy controls in more aspects than relatively active CFS patients do. This might for instance be the case regarding physical fitness, the impact of exercise on symptoms, and the accompanying cognitions such as the fear that activity is harmful. It is conceivable, but still to

be proved, that physical fitness is a process variable in the treatment of pervasively passive CFS patients. Although presumed, it is yet unknown whether a fear of activity is only prevalent and important for passive CFS patients, and not for the relatively active CFS patients. Furthermore, it might be important to know whether the level of physical activity has to be increased after treatment for the pervasively passive CFS patients only. For the other CFS patients successful treatment may not have to be accompanied with an increased level of physical activity. Finally, although we have developed a separate treatment protocol for pervasively passive CFS patients, its effect still has to be demonstrated.

The effect of different forms of CBT for CFS, such as CBGT, self-help, or inpatient treatments, as well as whether these forms of CBT are only effective for subgroups of patients is still unknown. Furthermore, whether different health professionals, such as a GP, can deliver CBT for CFS to subgroups of patients has to be subject of further study. And finally, before generalising the CBT for CFS treatment to other unexplained somatic syndromes or to fatigue in other conditions, studies on similarities and differences in the perpetuating factors in these syndromes will have to be accomplished.

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Summary

Summary

Chronic fatigue syndrome is defined as 'an unexplained persistent or relapsing chronic fatigue that is not the result of ongoing exertion, is not substantially alleviated by rest, and results in a substantial reduction in previous levels of occupational, educational, social, or personal activities'. Since 1990, the Nijmegen Fatigue Research Group (NFRG), a collaboration of the Departments of General Internal Medicine, Medical Microbiology and Medical Psychology of the University Medical Centre St Radboud Nijmegen (UMCN), has been involved in research on chronic fatigue syndrome. Studies in the current thesis are all related to the development of the treatment manual 'Cognitive Behaviour Therapy (CBT) for Chronic Fatigue Syndrome (CFS)'. In ***chapter 1*** a general introduction to the studies is given.

In ***chapter 2*** a study on the prevalence of CFS in the Netherlands, as recognized by general practitioners (GPs), is presented. Prevalence studies on CFS are rare, and the prevalence of CFS in the Netherlands was unknown. Prevalence data are important to assess disease burden and give directions for health policy. Furthermore, a GP can play an important role in CFS. If GPs diagnose CFS and acknowledge the patients complaints, further medicalisation can be prevented and ways for better management can be discussed. Because a cause for CFS has not been found and the diagnosis is established by means of exclusion, not all GPs accept CFS as a disease. Therefore, studying the prevalence of CFS in general practice was not only aimed at gaining insight into the number of CFS patients as recognized by GPs, but it also created the opportunity to inform all GPs about the existence of CFS. To prevent patients with Primary Fibromyalgia Syndrome (PFS) to be reported as CFS patients, the prevalence of PFS was stu-died at the same time. All 6657 GPs in the Netherlands received a mailed questionnaire, of which 60% was returned. Through extrapolation we found that in the Netherlands about 112 per 100 000 inhabitants were recognized by GPs as CFS and 157 per 100 000 as PFS patients. We argued that the found prevalence of CFS was a minimal estimate, especially because CFS was relatively unknown among GPs.

In several studies hypotheses on why CFS patients become and remain so tired have been tested. Gradually it became clear that in CFS facilitating, initiating and perpetuating factors should be distinguished. Little is known about facilitating factors. The initiating factors are most likely heterogeneous: infection, anaesthesia, operation and psychotrauma might play a role. Most is known about the perpetuating factors of symptoms and disabilities. Several studies revealed that cog-

nitions and behaviour are important perpetuating factors in CFS. Still, the question remained whether physiological processes could play a causal or perpetuating role in CFS. In this thesis two studies on possible physiological processes underlying CFS are presented. In ***chapter 3*** a study on the role of hyperventilation is reported. Because hyperventilation can produce substantial fatigue, and because clinical observations suggested that at least some CFS patients also fulfilled criteria for Hyperventilation Syndrome (HVS), it seemed worthwhile to investigate their relationship. In our study on CFS and hyperventilation, CFS patients, non-CFS patients known to experience hyperventilation, and healthy controls were compared on fatigue symptoms and symptoms indicative for HVS. Both CFS patients and the non-CFS patients known to experience physiological hyperventilation reported extreme fatigue and HVS symptoms, both groups to a similar degree. Physiological evidence of hyperventilation was found in 59% of the CFS patients. This was significantly more often than in healthy controls, of whom 22% showed physiological evidence of hyperventilation. However, no significant differences between CFS patients with and without physiological hyperventilation were found on severity of fatigue, impairment, number of complaints, activity level, psychopathology and depression. It is therefore concluded that physiological hyperventilation in CFS does not play a substantial perpetuating role and should be regarded as an epiphenomenon.

The second study on a possible physiological process in CFS concerns the role of physical deconditioning (***chapter 4***). CFS patients often complain that physical exertion produces an increase of complaints, leading to a greater need of rest and more time spent in bed. It has been suggested that this is due to a poor physical fitness and that physical deconditioning is a perpetuating factor in CFS. Studies on physical deconditioning in CFS so far had shown inconsistent results. In our study 20 CFS patients and 20 matched neighbourhood controls performed a maximal exercise test with incremental load. Heart rate, blood pressure, respiratory tidal volume, oxygen saturation, oxygen consumption, carbon dioxide production, and blood-gas values of arterialized capillary blood were measured. Physical fitness was quantified as the difference between the actual and predicted ratios of maximal workload versus increase of heart rate. Fatigue, impairment and physical activity were assessed to study their relationship with physical fitness. The results showed that CFS patients and their controls did not differ in physical fitness. Nine CFS patients even had a better fitness than their control. In both groups a negative relationship between physical fitness and fatigue was found. For CFS patients a negative correlation between fitness and impairment and a positive correlation between fitness and physical activity were found as well. Finally, it was found that more CFS patients than controls did not achieve a physiological limitation at maximal exercise. To put it briefly, in all subjects a worse physical fitness went together with more fatigue. The only difference found was that in CFS patients a worse physical fitness was also related to more impairment and less physical activity. Because no differences were found in physical fitness between CFS patients and their controls, we concluded that physical deconditioning is not likely to be a perpetuating factor in CFS. Finally, the

fact that CFS patients quitted the exercise at an earlier stage than their controls, while there was no physiological reason to stop the exercise, also suggests that other than physiological reasons determine a lower level of physical activity in CFS.

Many CFS patients complain that after physical exercise their symptoms increase and that their level of activity decreases, but the actual effect of exercise on symptoms and activity in CFS was unclear. The idea that exercise is harmful, however, may produce behaviour, such as inactivity, that may contribute to the perpetuation of CFS. Therefore we examined the effects of exercise on symptoms and activity in CFS, which study is presented in ***chapter 5***. The 20 CFS patients and 20 neighbourhood controls used in the former study were the subjects for this study as well. They all performed an incremental exercise test until exhaustion. Data on symptoms and activity were obtained from three days before the maximal exercise test up to five days thereafter. Data were collected every hour on the day before, the day of and the day after the exercise test,. Fatigue, muscle pain, minutes spent resting and the level of physical activity were assessed with a self-observation list. Physical activity was also assessed with an actometer. Compared with baseline, CFS patients became and remained more fatigued up to two days after the exercise test, whereas for controls self-observed fatigue returned to baseline after two hours. Concerning physical activity, either self-observed or actometer recorded, exercise did not induce any changes at all, neither for CFS patients nor for controls. This finding is not congruent with the reported minutes resting. Both CFS patients and controls reported that, compared with baseline, they spent more minutes resting on the day before as well as on the day after the maximal exercise test. Only CFS patients reported more minutes resting on the day of the exercise test. In sum, fatigue in CFS patients increased more after exercise compared both with their own baseline and controls. However, the level of actual physical activity remained unchanged for both groups.

No evidence was found that physiological processes were involved in the perpetuation of CFS, but more and more studies proved cognitive and behavioural factors to play an important perpetuating role in CFS. These findings suggested a promising role for cognitive behaviour therapy (CBT) in CFS. Therefore, after successful preliminary individual treatments of CFS patients, controlled studies on the effect of CBT were set up. In this thesis two studies on this subject are presented: the first concerning cognitive behaviour group therapy (CBGT), the second individual CBT (***chapter 6*** and ***chapter 7***).

Aim of the first CBT study was to investigate the effect of CBGT in an unselected group of CFS patients (***chapter 6***). Pre-treatment characteristics of CFS patients who improved after CBGT were compared with those of non-improved CFS patients to explore if CBGT was only effective for a subgroup of CFS patients. In a wait list controlled design 31 patients were allocated to CBGT, and 36 to the wait list condition. Our CBGT consisted of 12 two-hour sessions dur-

ing six months. Only a moderate effect on fatigue in favour of CBGT was found. For functional impairment the effect was opposite to what was expected. Patients improved after CBGT had fewer complaints at baseline compared to non-improved patients. Explanations for this moderate effect might be that during CBGT rest and relaxation were too much emphasised, that an unselected group of CFS patients was included and that therapists inexperienced with CB(G)T for CFS participated. Suggestions to improve CBGT for future research are given.

In our individual CBT for CFS study (***chapter 7***) the applicability of this treatment outside specialised settings is questioned. In this study CBT is compared with guided support groups and the natural course in a randomised trial at three centres. 278 patients diagnosed with CFS were randomly assigned to CBT (administered by 13 therapists recently trained in this technique for CFS), the support group approach or the natural course. Multidimensional assessments were done at baseline, 8 months and 14 months. The primary outcome variables were fatigue severity and functional impairment. Data were analysed by intention to treat. CBT was significantly more effective than both control conditions for fatigue severity and for functional impairment. Support groups were no more effective for CFS patients than the natural course. Prognostic factors for outcome after CBT were a higher sense of control predicting more improvement, a passive activity pattern and focusing on bodily symptoms predicting less improvement. It was concluded that, in a multicentre trial with many therapists, CBT was more effective than guided support groups and the natural course. A fundamental finding was that our treatment manual used in this study was effective for the so-called relatively active CFS patients, but not for the passive CFS patients.

Now that individual CBT for CFS proved to be effective, we wanted to know to what extent therapists complied with the various aspects of the treatment manual during the actual sessions and what their judgment was about the suitability of the treatment for transfer. Our aim was not only to have an integrity check for the study, but also to use this information to further refine the treatment manual. In our individual CBT for CFS study 13 therapists applied CBT to 82 CFS patients. In the study presented in ***chapter 8*** therapists' adherence and perceptions of the manual are investigated. Audio taped sessions were conducted to verify the therapists' adherence. Following completion of the study the therapists were asked to fill in a questionnaire. Analyses of the audio tapes showed that in 87% of the sessions the therapists adhered to the protocol. The questionnaire revealed that the therapists found it more difficult to treat patients with CFS than patients with psychological or other somatic problems. Treatment aspects posing most difficulties were integrating individual problems into the standardized treatment, dealing with the patient's lack of confidence in the treatment and handling insufficient motivation. Based on these study results the treatment manual has been revised. The treatment manual gives insight into the function analysis of the CFS patient. Making a further specified function analysis of each individual patient, in which the perpetuating factors of the particular patient

are further concretised, is now explicitly part of the manual. Consequently the treatment of each patient is individualised.

Following the results of the studies in this thesis, other NFRG studies and the international literature on CFS, the manual 'CBT for CFS' is adapted regularly. In ***chapter 9*** the last version of the manual, 'CBT for relatively active and for passive CFS patients', is described. Fundamental for the treatment of all CFS patients is the distinction between facilitating, initiating and perpetuating factors. Although somatic factors might have initiated symptoms in CFS, they do not explain the persistence of fatigue. Perpetuating factors make the symptoms prolong. Cognitive behaviour therapy (CBT) for CFS focuses on these perpetuating factors. It has also been shown that the treatment should not be completely the same for all CFS patients. Based on their level of activity, two groups of patients can be distinguished. For so-called relatively active CFS patients the main perpetuating factors are non-accepting and demanding cognitions leading to bursts of activity. For so-called passive CFS patients the fear that activity might worsen their complaints, resulting in avoidance of activity, is the most important perpetuating factor. These differences in perpetuating factors resulted in partly separate treatment manuals for relatively active and passive CFS patients. In this chapter basic assumptions, considerations before starting CBT for CFS, and ways to determine the activity pattern are further elaborated upon. To conclude the differences in the treatments for relatively active and passive CFS patients are described.

The general discussion in ***chapter 10*** mainly concerns the consequences of our findings for the treatment of CFS patients. We reflect on what is essential in CBT for CFS, the role of physical activity, and the use of the manual. The distinction between passive and relatively active CFS patients turned out to be of major importance in the treatment of CFS. It is plausible that the role of physical fitness, a fear of activity and the need to actually increase the level of physical activity is different for passive and for relatively active CFS patients. However, individual CBT for CFS proved to be an effective treatment, especially for relatively active CFS patients. Future studies will have to determine whether different forms of CBT for CFS, such as CBGT, self-help, or inpatient treatments and the manual developed for passive CFS patients are effective as well.

Samenvatting

Samenvatting

Het chronisch vermoeidheidssyndroom wordt gedefinieerd als een 'onverklaarde voortdurende of terugkerende chronische vermoeidheid die niet het gevolg is van langdurende inspanning, die niet substantieel verminderd door rust, en die ernstige beperkingen in het dagelijks leven tot gevolg heeft'. Sinds 1990 houdt de 'Nijmeegse Fatigue Research Group' (NFRG), een samenwerkingsverband tussen de afdelingen Algemeen Interne Geneeskunde, Medische Microbiologie en Medische Psychologie van het UMC St Radboud, zich bezig met onderzoek naar het chronisch vermoeidheidssyndroom. De in dit proefschrift gepresenteerde studies zijn steeds op een of andere wijze verbonden aan de ontwikkeling van het behandelprotocol 'Cognitieve Gedragstherapie (CGT) voor het Chronisch Vermoeidheidssyndroom (CVS)'. ***Hoofdstuk 1*** behelst een algemene introductie op de verschillende studies.

In ***hoofdstuk 2*** wordt een onderzoek naar de prevalentie van CVS, zoals herkend door huisartsen, beschreven. De prevalentie van CVS was nog weinig onderzocht, en de prevalentie van CVS in Nederland was onbekend. Deze gegevens zijn van belang om de omvang van het probleem vast te stellen en geven richting aan gezondheidsbeleid. Ook de rol van de huisarts is belangrijk bij CVS. Wanneer een huisarts CVS diagnosticeert en de klachten van de patiënt erkent, kan verdere medicalisering worden voorkomen en kunnen andere manieren om met de klachten om te gaan worden besproken. Omdat een oorzaak voor CVS niet is gevonden, accepteren niet alle huisartsen CVS als een aandoening. Naast het onderzoeken van de prevalentie van CVS in de huisartsenpraktijk was ons doel om alle huisartsen te informeren over de criteria van CVS. Om te voorkomen dat patiënten met het Primaire Fibromyalgie Syndroom (PFS) als CVS patiënten zouden worden aangemerkt, werd tegelijkertijd de prevalentie van PFS onderzocht. Alle praktiserende huisartsen in Nederland kregen een vragenlijst opgestuurd. Hiervan werd 60% geretourneerd. Na extrapolatie werd gevonden dat 112 per 100 000 inwoners in Nederland door huisartsen werden herkend als CVS patiënten en 157 per 100 000 inwoners als PFS patiënten. We beargumenteerden dat de gevonden prevalentie een minimale schatting was, vooral omdat CVS nog relatief onbekend was onder huisartsen.

Waarom CVS patiënten zo moe worden alsook waarom ze zo moe blijven was en is onderwerp van vele studies. Uit onderzoek werd duidelijk dat bij CVS onderscheid gemaakt moet worden tussen faciliterende, initiërende en in stand houdende factoren. Over de faciliterende factoren is nog weinig bekend. De initiërende factoren zijn waarschijnlijk heterogeen. Infecties, anes-

thesie, operaties en psychotrauma's kunnen een uitlokkende factor zijn. Het meest is bekend over factoren die de symptomen en beperkingen van CVS in stand houden. Uit verschillende studies bleek dat cognities en gedrag hierbij van belang zijn. Toch bleef het de vraag of fysiologische processen niet ook een oorzakelijke of in stand houdende rol spelen. In dit proefschrift worden twee studies gepresenteerd die gaan over fysiologische processen en CVS. In ***hoofdstuk 3*** is een onderzoek naar de relatie tussen CVS en hyperventilatie beschreven. Hyperventilatie kan ernstige vermoeidheid tot gevolg hebben. Uit de klinische praktijk bleek dat in ieder geval enkele CVS patiënten ook voldeden aan criteria voor het Hyperventilatie Syndroom (HVS). In ons onderzoek werden CVS patiënten, niet-CVS patiënten die bekend waren met hyperventilatie volgens fysiologische criteria, verder hyperventilatie genoemd, en gezonde controles met elkaar vergeleken. Extreme vermoeidheid en symptomen van het HVS werden door CVS patiënten en niet-CVS patiënten met hyperventilatie in dezelfde mate gerapporteerd. Van de CVS patiënten bleek 59% te hyperventileren. Dit was significant vaker dan de gezonde controles, waarbij voor 22% hyperventilatie werd aangetoond. Voor wat betreft de ernst van vermoeidheid, de beperkingen, het aantal klachten, het activiteitenniveau, psychopathologie en depressie werden geen significante verschillen gevonden tussen CVS patiënten met en CVS patiënten zonder hyperventilatie. Op grond van deze bevindingen werd geconcludeerd dat hyperventilatie geen in stand houdende factor is bij CVS, maar beschouwd moet worden als een epifenomeen.

Een tweede fysiologisch proces dat een rol zou kunnen spelen bij CVS betreft de fysieke conditie (***hoofdstuk 4***). Veel CVS patiënten klagen dat door lichamelijke inspanning hun klachten toenemen waardoor ze daarna tot bijna niets meer in staat zijn. Een al lang bestaande hypothese was dat dit wordt veroorzaakt door een slechte fysieke conditie en dat een slechte fysieke conditie een in stand houdende factor van CVS zou kunnen zijn. Studies die de fysieke conditie van CVS patiënten onderzochten lieten inconsistente resultaten zien. In ons onderzoek, weergegeven in hoofdstuk 4, zijn 20 CVS patiënten vergeleken met 20 buurtcontroles. Alle proefpersonen ondergingen een maximale inspanningstest met toenemende belasting. Hierbij werden de hartslag, bloeddruk, ademteugvolume, zuurstofsaturatie, zuurstofconsumptie, koolzuurproductie, en bloedgaswaarden van gearterialiseerd capillair bloed gemeten. De lichamelijke conditie werd geoperationaliseerd als het verschil tussen de actuele en voorspelde ratios van de maximale werklast versus de toename in de hartfrequentie. Vermoeidheid, beperkingen en lichamelijke activiteit werden gemeten om hun relatie met de fysieke conditie te onderzoeken. Uit de resultaten bleek dat er geen verschil was in fysieke conditie tussen CVS patiënten en hun controles. Negen CVS patiënten hadden zelfs een betere fysieke conditie dan hun controle. In beide groepen werd een negatieve correlatie gevonden tussen fysieke conditie en vermoeidheid. Bij CVS patiënten werd tevens een negatief verband gevonden tussen fysieke conditie en beperkingen en een positief verband tussen fysieke conditie en lichamelijke activiteit. CVS patiënten stopten vaker dan controles met de inspanningstest zonder hun fysiologische grens te hebben bereikt. Omdat CVS patiënten geen slechtere fysieke conditie hadden dan hun controles,

concludeerden we dat het niet waarschijnlijk is dat fysieke deconditionering een in stand houdende factor is bij CVS. Het feit dat CVS patiënten eerder stopten met de inspanningstest dan hun controles, zonder dat er een fysiologische reden was om te stoppen, suggereert dat andere dan fysiologische redenen het lagere activiteitenniveau van CVS patiënten bepalen.

Veel CVS patiënten rapporteren dat na hevige lichamelijke inspanning hun klachten dagenlang zijn toegenomen en dat zij tot minder lichamelijke activiteit in staat zijn. Of het niveau van lichamelijke activiteit na een grote inspanning inderdaad dagenlang lager is dan daarvoor, was nooit aangetoond. Het idee dat inspanning schadelijk is kan gedrag zoals inactiviteit tot gevolg hebben, hetgeen CVS in stand kan houden. Daarom onderzochten we het effect van inspanning op de klachten en het lichamelijke activiteitenniveau van CVS patiënten (***hoofdstuk 5***). Aan dit onderzoek namen dezelfde 20 CVS patiënten en hun buurtcontroles deel als in het vorige onderzoek. Zij ondergingen allen een maximale inspanningstest tot uitputting. Data betreffende symptomen en activiteit werden gemeten drie dagen voor tot en met vijf dagen na de inspanningstest. Op de dag voor, de dag van en de dag na de inspanningstest werden de gegevens ieder uur verzameld. Vermoeidheid, spierpijn, het aantal minuten rust en het oordeel over de mate van lichamelijke activiteit werden gemeten met een zelfobservatielijst. Lichamelijke activiteit werd tevens gemeten met een actometer. De ervaren vermoeidheid van CVS patiënten was tot twee dagen na de inspanningstest verhoogd ten opzicht van de dagen voor de inspanningstest, de vermoeidheid van de controlegroep was twee uur na de inspanningstest weer op hetzelfde niveau als voor de inspanningstest. Het niveau van lichamelijke activiteit, zowel gemeten met de zelfobservatielijst als met de actometer, bleef na de inspanningstest vrijwel onveranderd ten opzichte van het niveau voor de inspanningstest. Dit gold zowel voor CVS patiënten als voor de controles. Deze bevinding is niet congruent met het aantal gerapporteerde minuten rust. Zowel CVS patiënten als controles rapporteerden dat zij een dag voor de inspanningstest en de dag na de inspanningstest meer rustten dan de andere dagen voor de inspanningstest. Alleen CVS patiënten rapporteerden ook meer te rusten op de dag van de inspanningstest. De belangrijkste conclusie van dit onderzoek was dat ondanks de toename in ervaren vermoeidheid deze toegenomen vermoeidheid na de inspanningstest geen gevolgen had voor de mate van lichamelijke activiteit.

In de hiervoor genoemde studies vonden wij geen bewijs dat fysiologische processen een rol speelden bij het in stand houden van CVS. Steeds meer studies toonden echter aan dat cognities en gedrag betrokken waren bij het in stand houden van CVS. Deze onderzoeksresultaten suggereerden een veelbelovende rol voor cognitieve gedragstherapie (CGT). Daarom is, na eerste positieve ervaringen met individuele CGT van CVS, wetenschappelijk onderzoek naar het effect van CGT voor CVS gestart. In dit proefschrift zijn hierover twee studies opgenomen. De eerste betreft het effect van groeps-CGT voor CVS, de tweede het effect van individuele CGT voor CVS (***hoofdstuk 6*** en ***hoofdstuk 7***).

Doel van de eerste CGT studie was om het effect te onderzoeken van groeps-CGT in een ongeselecteerde groep van CVS patiënten (***hoofdstuk 6***). In een wachtlijst gecontroleerd onderzoek werden 31 patiënten toegewezen aan de groeps-CGT en 36 aan de wachtlijstconditie. De groeps-CGT bestond uit 12 sessies van twee uur in een periode van 6 maanden. Er werd slechts een matig effect gevonden op vermoeidheid in het voordeel van groeps-CGT. Voor wat betreft de beperkingen in het dagelijks leven was het effect tegenovergesteld van hetgeen werd verwacht. Voor de patiënten in de wachtlijstconditie waren de beperkingen na 6 maanden afgenomen. Voor de patiënten die aan de groeps-CGT hadden deelgenomen niet. Om te achterhalen of groeps-CGT alleen effectief was voor een subgroep van CVS patiënten werden CVS patiënten die verbeterden na de groeps-CGT vergeleken met CVS patiënten die niet verbeterden na groeps-CGT op hun kenmerken bij de baseline meting. Uit deze analyses bleek dat patiënten die verbeterd waren na groeps-CGT bij baseline minder klachten hadden dan de patiënten die niet verbeterd waren.
Verklaringen voor het geringe effect van de groeps-CGT zouden kunnen zijn dat in de behandeling rust en ontspanning teveel werden benadrukt, dat de behandeling aan een ongeselecteerde groep patiënten werd aangeboden en dat therapeuten die nog onervaren waren met (groeps-)CGT de behandeling uitvoerden. Suggesties om de groeps-CGT te verbeteren voor toekomstig onderzoek werden besproken.

In de individuele CGT voor CVS studie (***hoofdstuk 7***) is de mogelijkheid om deze behandeling toe te passen in andere dan in CVS gespecialiseerde centra onderzocht. In deze studie werd CGT vergeleken met lotgenotencontactgroepen en de gangbare praktijk, in een gerandomiseerd onderzoek. De behandelingen vonden plaats in drie verschillende centra. In dit onderzoek participeerden 278 CVS patiënten. Deze patiënten werden random toegewezen aan de CGT conditie, de lotgenotencontactgroepen of de gangbare praktijk conditie. De CGT behandelingen werden uitgevoerd door 13 therapeuten, onervaren met de behandeling van CVS patiënten. Zij werden van te voren getraind in 'CGT voor CVS'. Tijdens het uitvoeren van de behandeling kregen zij supervisie. Multidimensionele metingen vonden plaats bij baseline, bij 8 en bij 14 maanden. De primaire uitkomstmaten waren vermoeidheid en beperkingen in het dagelijks leven. De resultaten lieten zien dat CGT significant effectiever was dan de beide controle condities, zowel voor wat betreft vermoeidheid als voor wat betreft beperkingen. Lotgenotencontact was niet effectiever dan de gangbare praktijk. Een positieve self-efficacy (het idee dat men zelfs iets aan de klachten kan doen) voorspelde meer verbetering na CGT. Een passief activiteitenpatroon en een sterke gerichtheid op lichamelijke symptomen voorspelden minder verbetering na CGT. Een belangrijke bevinding was dat het in dit onderzoek gebruikte behandelprotocol effectief was voor de zogenaamde relatief actieve CVS patiënten, maar niet voor de passieve CVS patiënten. Een belangrijke conclusie was dat CGT voor CVS ook effectief uitgevoerd kon worden door therapeuten die tot dan toe geen ervaring hadden met deze behandeling.

Nu individuele CGT voor CVS effectief was gebleken, wilden we weten in welke mate de therapeuten de behandeling ook daadwerkelijk volgens protocol hadden uitgevoerd. Daarnaast wilden we weten in hoeverre de therapeuten van oordeel waren dat de behandeling kon worden overgedragen. Doel van dit onderzoek was niet alleen om een integrity check te hebben voor de individuele CGT voor CVS studie, maar ook om de verzamelde informatie te gebruiken om het behandelprotocol te verbeteren. In ***hoofdstuk 8*** wordt een studie beschreven waarin deze vragen worden onderzocht. Aan de individuele CGT voor CVS studie deden 13 therapeuten mee die samen de CVS patiënten in de CGT conditie behandelden. Uitgewerkte audio-opnamen van de sessies werden gebruikt om de mate waarin de therapeuten zich aan het protocol hadden gehouden te onderzoeken. Aan het einde van de studie vulden de therapeuten een vragenlijst in. Uit de analyses van de audio-opnamen bleek dat in 87% van de sessies de therapeuten zich aan het behandelprotocol hadden gehouden. Dit wordt beschouwd als een goed resultaat. Uit de vragenlijst bleek dat therapeuten het moeilijker vonden om CVS patiënten te behandelen dan om patiënten met psychische of andere somatische klachten te behandelen. Aspecten van de behandeling die de meeste problemen opleverden waren het integreren van individuele problemen in een gestandaardiseerde behandeling, het omgaan met een gebrek aan vertrouwen in de behandeling van patiënten, en het omgaan met onvoldoende motivatie van de patiënt. Op grond van deze onderzoeksresultaten is het behandelprotocol aangepast. Het protocol geeft inzicht in de functieanalyse en behandeling van de CVS patiënt. Het maken van een verder gespecificeerde functieanalyse voor iedere individuele patiënt, waarin de in stand houdende factoren van deze patiënt verder worden geconcretiseerd, is nu expliciet onderdeel van het protocol. Hiermee wordt de behandeling verder op het individu toegespitst.

Op grond van de resultaten van de studies in dit proefschrift, van andere studies van de NFRG en de internationale literatuur, is het protocol 'CGT voor CVS' regelmatig aangepast. In ***hoofdstuk 9*** wordt de huidige versie van het protocol, 'CGT voor relatief actieve en voor passieve CVS patiënten' beschreven. Essentieel voor de behandeling van alle CVS patiënten is het onderscheid tussen faciliterende, initiërende en in stand houdende factoren. Hoewel somatische factoren een rol kunnen hebben gespeeld bij het ontstaan van CVS, bieden zij geen verklaring voor het blijven voortbestaan van de vermoeidheid. Het zijn de in stand houdende factoren die maken dat de vermoeidheid niet overgaat. CGT voor CVS richt zich op deze in stand houdende factoren. Op basis van hun activiteitenniveau kunnen twee groepen patiënten worden onderscheiden. Voor de zo genoemde relatief actieve CVS patiënten zijn de belangrijkste in stand houdende factoren niet-accepterende en eisende cognities, die leiden tot pieken van activiteit. Voor de zo genoemde passieve CVS patiënten is de angst dat activiteit de klachten verergerd, resulterend in het vermijden van activiteit, de meest belangrijke in stand houdende factor. Dit verschil in in stand houdende factoren heeft geresulteerd in twee gedeeltelijk verschillende behandelprotocollen. Eén voor relatief actieve en één voor passieve CVS patiënten. In ***hoofdstuk 9*** zijn de basis assumpties, overwegingen voor het starten van de behandeling 'CGT voor CVS' en de wijze waarop het

activiteitenpatroon kan worden vastgesteld, beschreven. Daarna worden de verschillen in de behandelingen voor relatief actieve en voor passieve CVS patiënten uiteengezet.

De algemene discussie in ***hoofdstuk 10*** gaat vooral over de consequenties van de onderzoeksbevindingen voor de behandeling van CVS patiënten. Gereflecteerd wordt op wat nu essentieel is in de CGT behandeling van CVS, op de rol van lichamelijke activiteit en op het gebruik van het behandelprotocol. Het onderscheid tussen passieve en relatief actieve CVS patiënten is van groot belang gebleken voor de behandeling. Het is denkbaar dat de rol van lichamelijke activiteit, angst voor activiteit en de noodzaak om het daadwerkelijke activiteitenniveau te verhogen verschillend is voor passieve en voor relatief actieve CVS patiënten. Individuele 'CGT voor CVS' bleek een effectieve behandeling, vooral voor de relatief actieve CVS patiënten. Toekomstig onderzoek zal moeten uitwijzen of verschillende vormen van CGT voor CVS, zoals groeps-CGT, zelf hulp instructies, of klinische behandeling als ook of het laatste behandelprotocol dat is aangepast voor passieve CVS patiënten, eveneens effectief zijn.

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Dankwoord

Dankwoord

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Curriculum vitae

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Ellen Bazelmans werd op 8 maart 1966 geboren te Roosendaal en Nispen. In 1984 behaalde zij haar VWO diploma aan het Rythoviuscollege te Eersel. In 1990 rondde zij haar studie psychologie af aan de Katholieke Universiteit Nijmegen, met als afstudeerrichting Klinische Psychologie. Van 1990 tot en met 1993 was zij werkzaam op de Sint Maartenskliniek in Nijmegen. Eerst als onderzoeker, later in de patiëntenzorg. Van 1993 tot en met 2000 werkte zij als psycholoog in de patiëntenzorg op de afdeling Medische Psychologie van het Deventer Ziekenhuis.

Naast deze werkzaamheden begon zij in 1992 op de afdeling Medische Psychologie van het Universitair Medisch Centrum (UMC) St Radboud te Nijmegen. Haar werkzaamheden waren aanvankelijk vooral gericht op de patiëntenzorg en het verkrijgen van haar registratie als gedragstherapeut (1997) en rationeel emotief therapeut (1998). Vanaf 1994 begon zij ook als onderzoeker werkzaamheden te verrichten. Zij was verder betrokken bij het schrijven van de onderzoeksaanvraag voor ontwikkelingsgeneeskunde 'Cognitieve gedragstherapie voor het Chronisch Vermoeidheidssyndroom'. Gedurende de uitvoerende fase van dit onderzoeksproject, van 1996 tot en met 1998, was zij mede verantwoordelijk voor het ontwikkelen en overdragen van het behandelprotocol. Van 1999 tot en met 2001 werkte zij als 'protocol ontwikkelaar', trainer en supervisor op het project 'Psychische Vermoeidheid in de arbeidssituatie: een interventie door huisartsen'. In 2002 en 2003 werkte zij als 'protocol ontwikkelaar' en als therapeut op het project vermoeidheid na kanker.

Vanaf 2000 werkt zij full-time bij het UMC St Radboud. Naast haar werk in onderzoeksprojecten en onderwijstaken, is zij werkzaam voor de patiëntenzorg van verschillende Inwendige Specialismen. Van 2000 tot 2002 was zij gedetacheerd op het Universitair Longcentrum Dekkerswald. In 2001 kreeg zij extra onderwijstaken ten behoeve van het curriculum geneeskunde.

In 1999 behaalde zij haar BIG registratie GZ-psycholoog, in 2001 haar BIG registratie psychotherapeut en in 2004 haar registratie als supervisor en leertherapeut van de Vereniging voor Gedragstherapie en Cognitieve Therapie.

Ellen Bazelmans leeft samen met Yvonne Keurentjes.